Special Lecture 1 : The finding, development and progress of potassium channel openers

The 87th Annual Meeting of The Japanese Pharmacological Society
Sendai, 20140319, 10:45-11:45

Special Lecture 1

The finding, development and progress of potassium channel openers.

Teruyuki YANAGISAWA, MD, PhD
Dept. Mol. Pharmacol.,
Tohoku Univ. Sch. Grad. Med.

☑ The author has no conflict of interest to disclose with respect to this presentation.

日本薬理学会
The Japanese Pharmacological Society

The development of nicorandil (SG-75)

The development of nicorandil (SG-75) was started under the concept "**a nitrate-like antianginal drug without hypotensive side effect**". During the studies to explore the mechanism of action of nicorandil, it has been revealed that nicorandil opens potassium (K^+) channel and that ATP-sensitive K^+ channels (K_{ATP}) are the target molecules, which are also opened by other K^+ channel openers (KCO) as antihypertensives. Although the clinical results related with pure KCOs for hypertension have been failed, nicorandil which is a hybrid of nitrate and KCO has been successful as a drug for angina pectoris, acute myocardial infarction and acute heart failure. We have also suggested that nicorandil will be effective in managing pulmonary arterial hypertension. The KCOs targeting other than K_{ATP} are expected to be novel therapeutic agents to control pain or epilepsy, including many pathological situations.

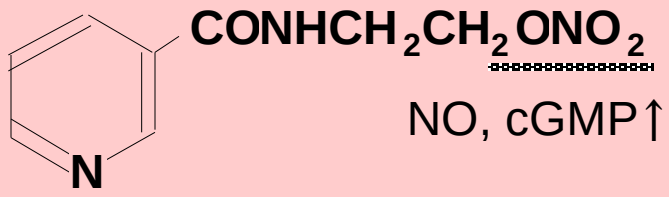
K^+ channel openers (K_{ATP}COs)

- Historical points of view
- Why they are **not** successful for the antihypertensive agents?
- Vasospastic angina
- Hyperpolarization-relaxation coupling
- Progress of new types KCOs

K^+ channel openers

Pyridine: **nicorandil**

KRN2391

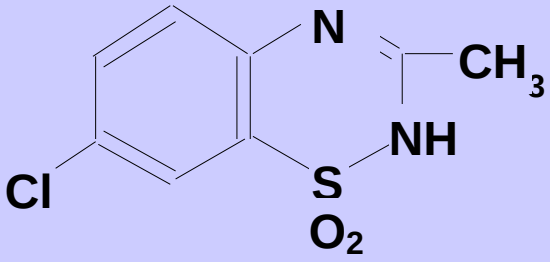


NO, cGMP↑

"N-K hybrid"

Benzothiadiazine:

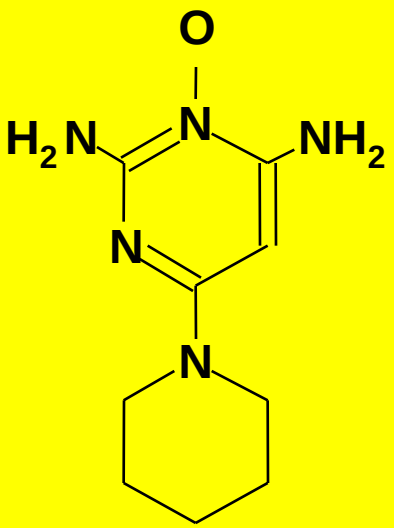
diazoxide



"Nonspecific KCO"

Pyrimidine:

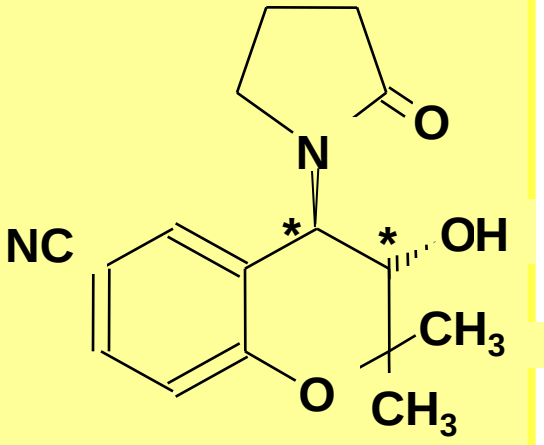
minoxidil, LP 805



trichogen

Benzopyran:

Cromakalim



Hyperglycemia
(side effect)
Insulin secretion↓
K_{ATP} open in β cell

Hypertricosis
as a side effect

cf. ischemic preconditioning;
pharmacological

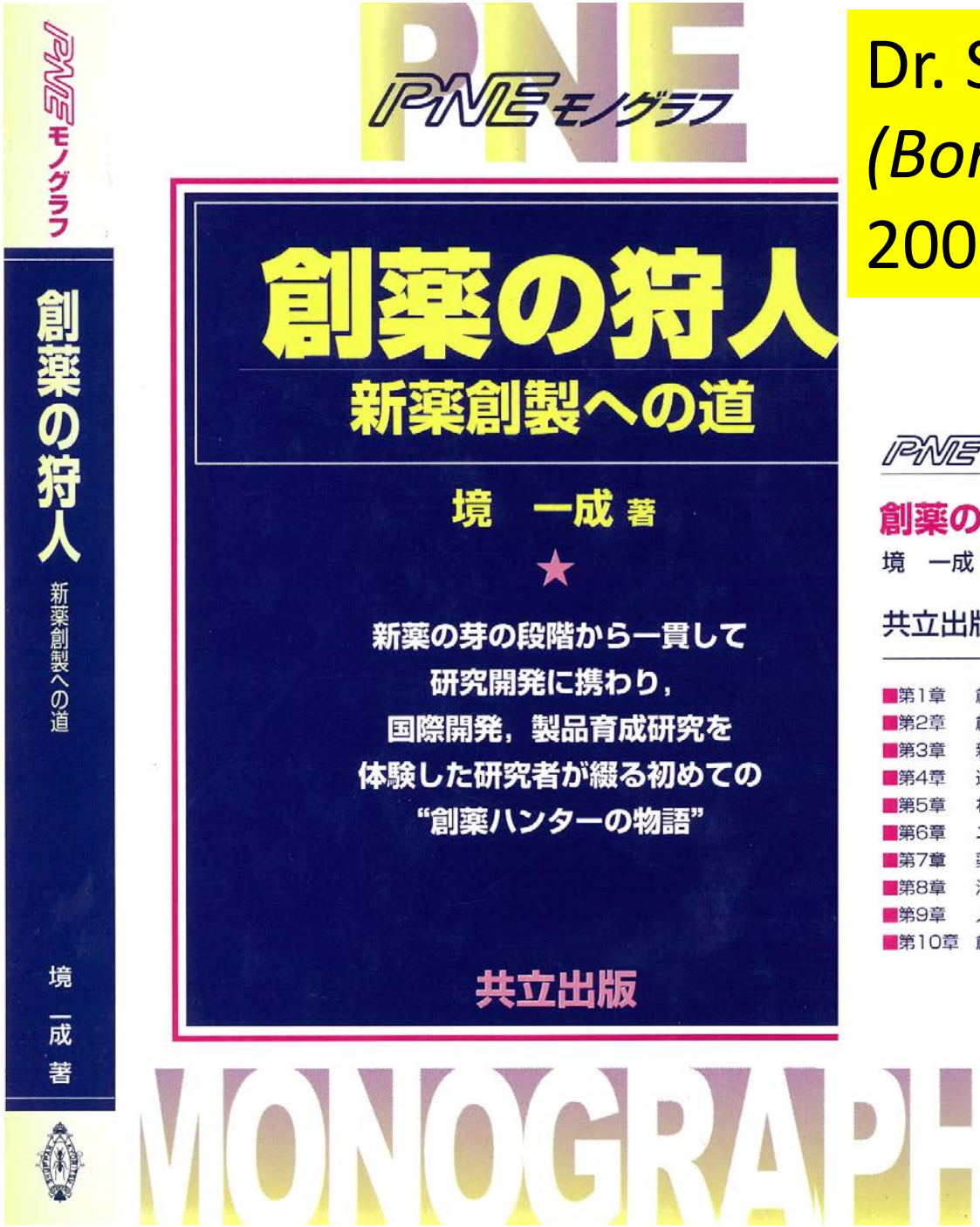
The development of nicorandil (SG-75)

- Blood-perfused cardiac preparations in Tohoku University
- The serendipity to find K^+ opening activity

Hashimoto, Koroku

Taira, Norio

東北大学



Dr. Sakai, K
(Born in Ishinomaki)
2000年11月

ISBN4-320-05499-7
C3045 ¥3000E

PNEモノグラフ 定価（本体3,000円+税）

創薬の狩人 新薬創製への道

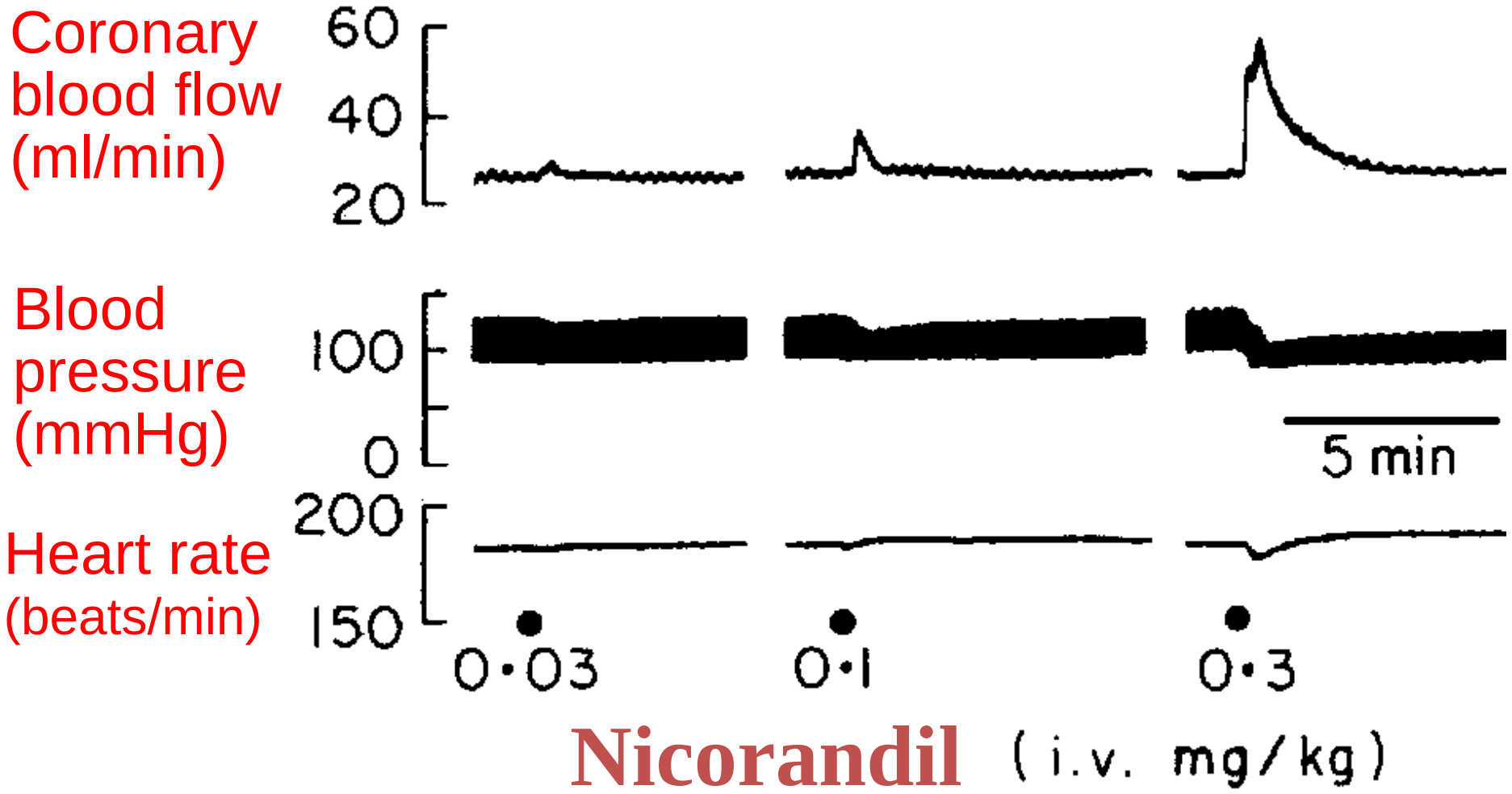
境 一成 著

共立出版株式会社

The Development of nicorandil

a nitrate-like antianginal drug without hypotensive side effect

Increase in coronary flow by nicorandil



Modified from **Taira N et al. Clin Exp Pharmacol Physiol 1979; 6:301-316.**

i. v.: intravenous injection

Nicorandil (SG-75): coronary resistance↓

Intraduodenal administration of nicorandil (3mg/kg)
≒ intravenous injection (0.3mg/kg)

	Basal value	Value after SG-75*
Coronary sinus outflow (ml/min)	21.6 (3.0)	40.4 (5.0)†
Mean blood pressure (mmHg)	89 (6)	53 (8)†
Coronary resistance (mmHg min/ml)	4.5 (0.8)	1.5 (0.4)†
Coronary a.v. O_2 difference (vol.%)	12.1 (0.04)	6.9 (0.9)†
Myocardial O_2 consumption (ml/min per 100 g)	4.1 (0.7)	4.4 (0.8)
Heart rate (beats/min)	180 (15)	170 (3)†
AV Conduction time (ms)	100 (2)	98 (1)

†: $P < 0.05$, SEM in parentheses, n=5.

a.v.: arterio-venous; AV: atrioventricular

Taira N, Satoh K, Yanagisawa T et al. Clin Exp Pharmacol Physiol 1979;6:301-16.

Nicorandil (SG-75): coronary resistance↓

Coronary resistance 4.5 → 1.5

Change In the systemic resistance: −40%

Coronary sinus outflow (ml/min)	21.6	(3.0)	40.4	(5.0)†
Mean blood pressure (mmHg)	89	(6)	53	(8)†
Coronary resistance (mmHg min/ml)	4.5	(0.8)	1.5	(0.4)†
Coronary a.v. O_2 difference (vol.%)	12.1	(0.04)	6.9	(0.9)†
Myocardial O_2 consumption (ml/min per 100 g)	4.1	(0.7)	4.4	(0.8)
Heart rate (beats/min)	180	(15)	170	(3)†
AV Conduction time (ms)	100	(2)	98	(1)

†: P＜0.05, SEM in parentheses, n=5.

a.v.: arterio-venous; AV: atrioventricular

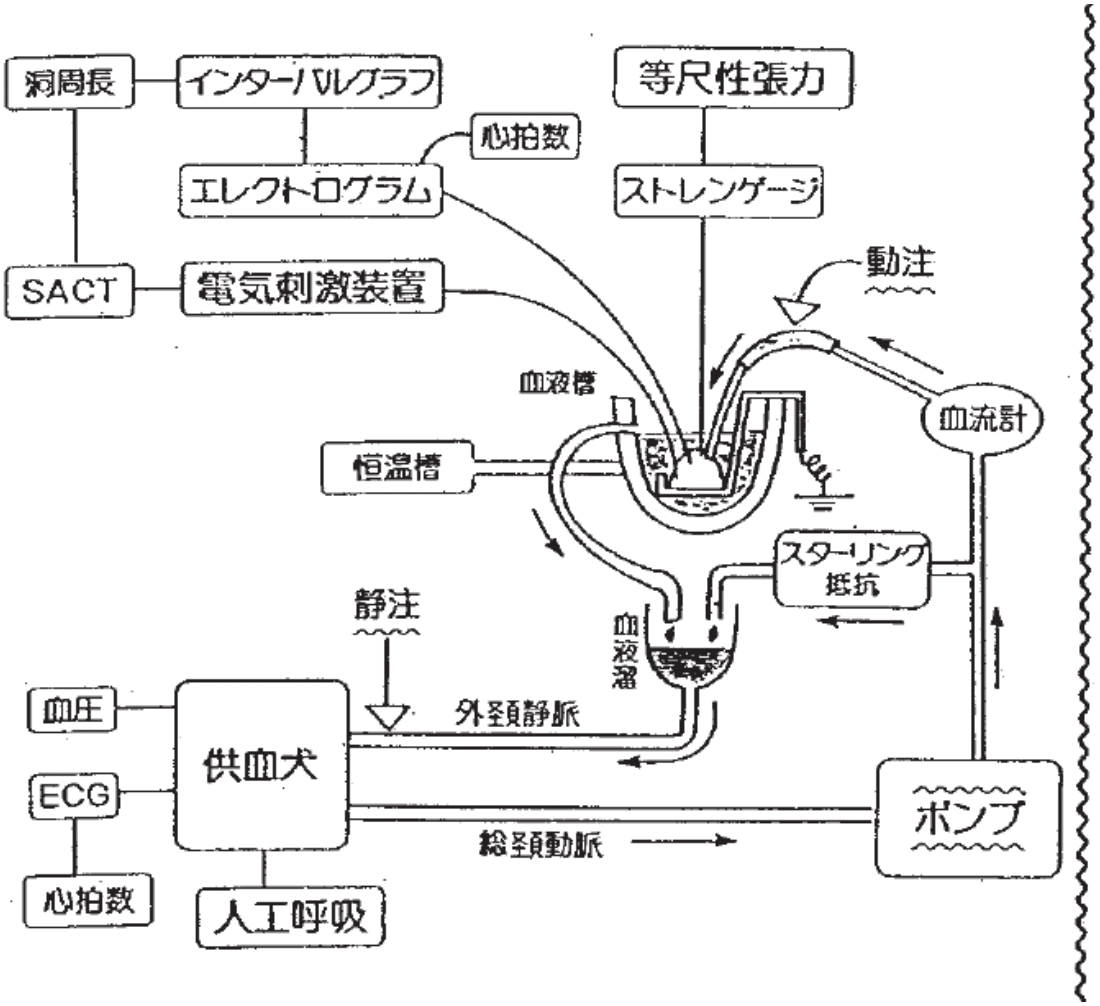
Taira N, Satoh K, Yanagisawa T et al. Clin Exp Pharmacol Physiol 1979;6:301-16.

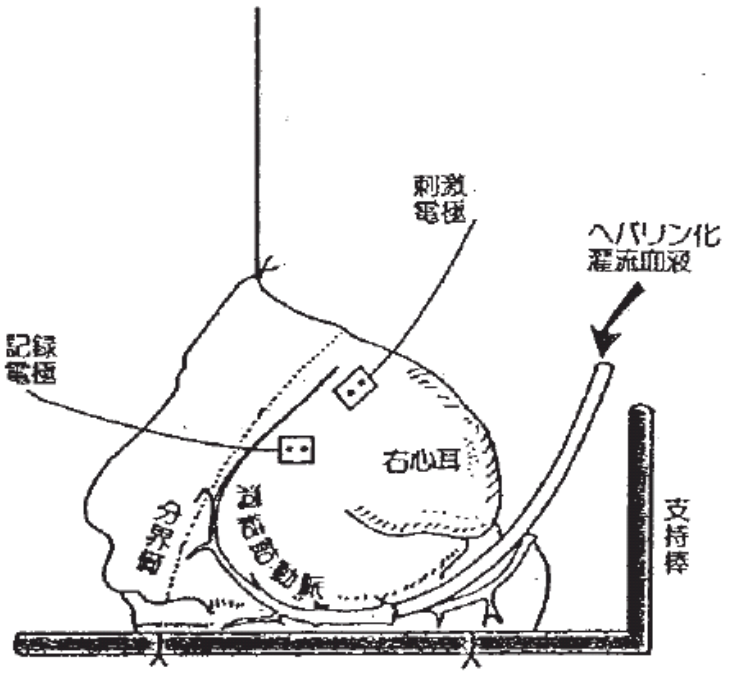
Distribution of cardiac output & O_2 consumption in organs at rest

Organs	Blood flow (mL/min)			O_2 consumption	
	(/100g)	(Whole)	(%)	(mL/min)	(%)
Brain	57	750	15	46	20
Heart	70	200	4	27	11
Liver	95	1,350	27	33	14
Kidney	420	1,200	24	16	7
Sk. muscle	3	850	16	70	30
Skin	7	350	7	5	2
Others		400	7	36	16
Total		5,100	100	233	100

In heart, the tissue O_2 partition pressure is low,
thus the organ is under relatively hypoxic condition.
K_{ATP} channels are seemed to be easily opened in heart.

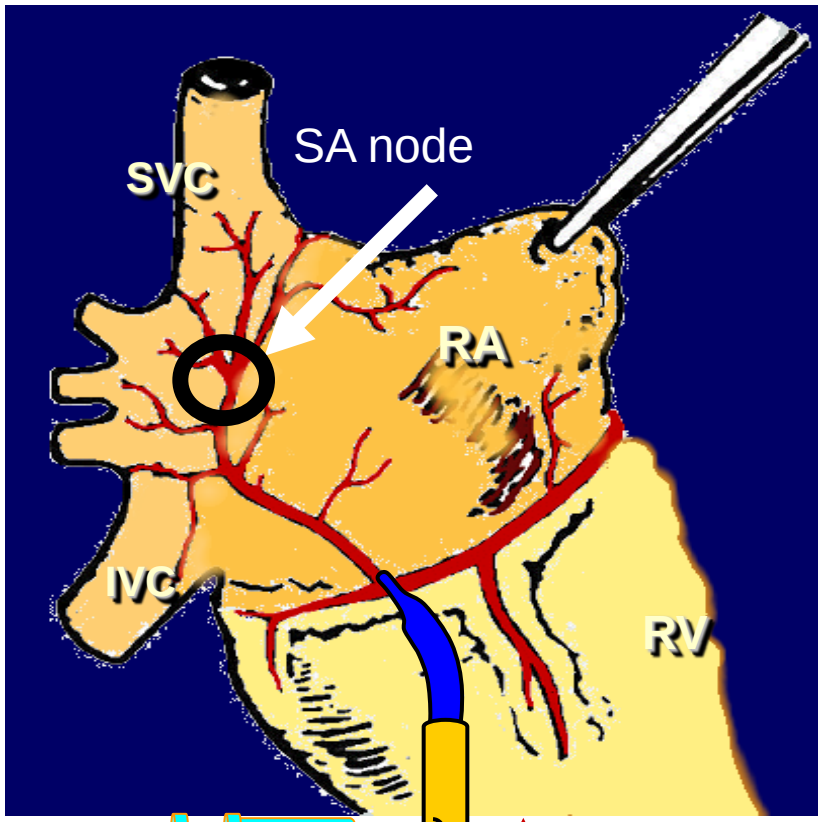
Isolated blood-perfused cardiac preparations





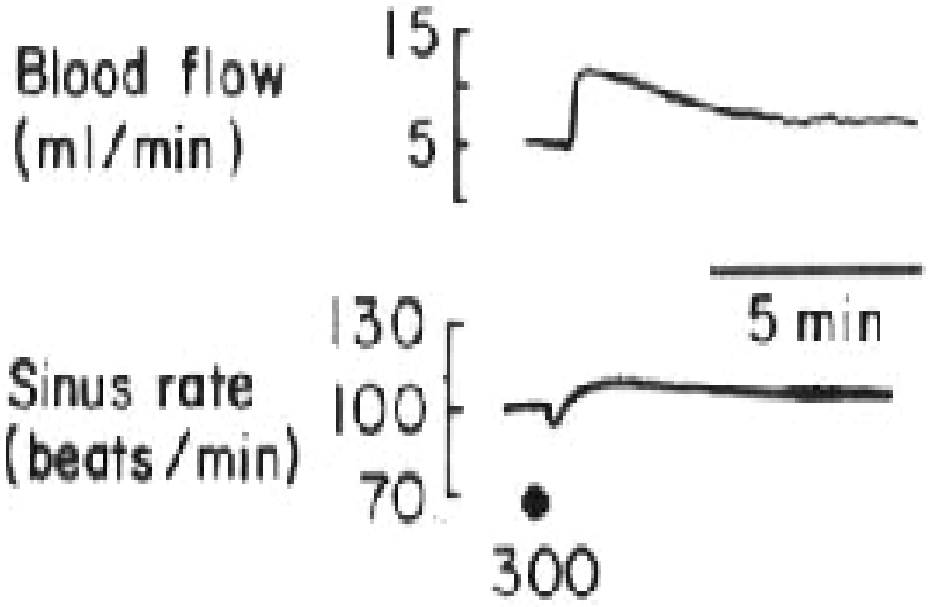
https://soar-ir.shinshu-u.ac.jp/dspace/bitstream/10091/9330/1/Shinshu_Med51-2-02.pdf

Increase in coronary blood flow, Very llittle effect on sinoatrial (SA) rate



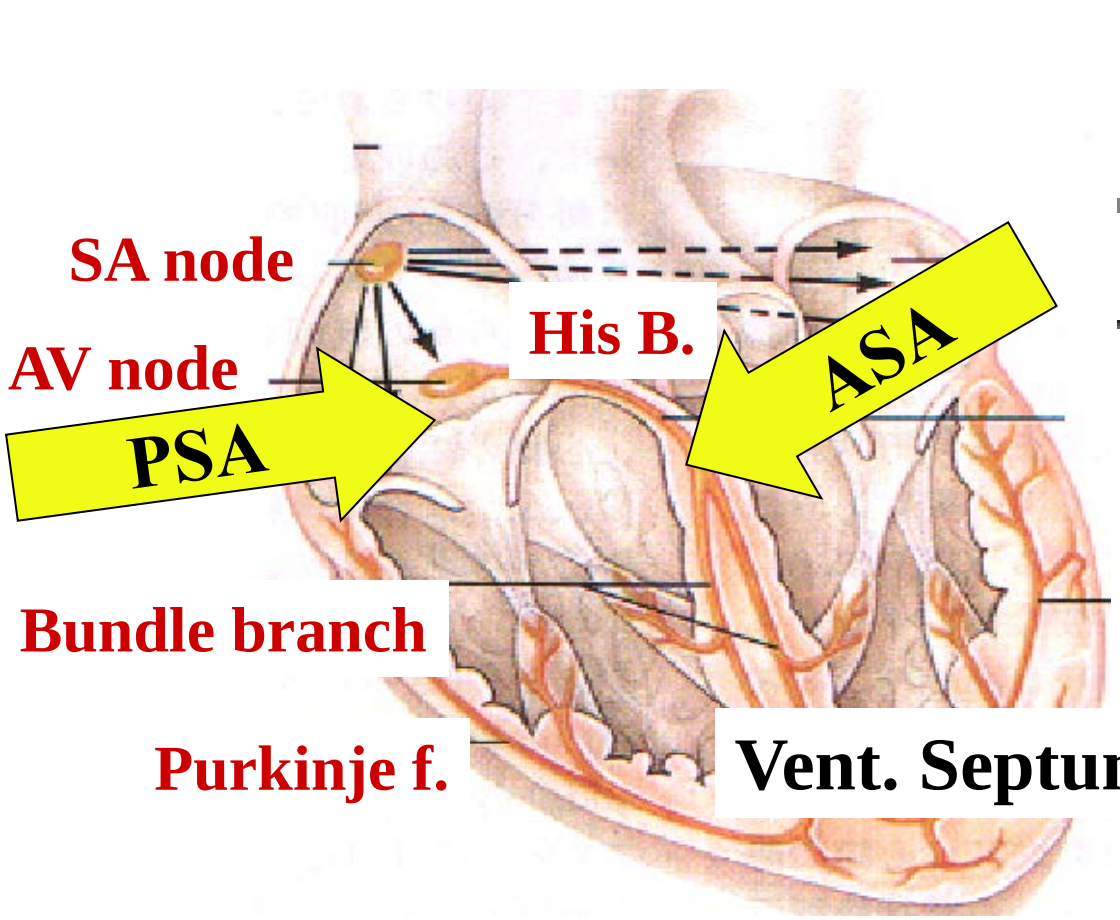
Injection, i. a.

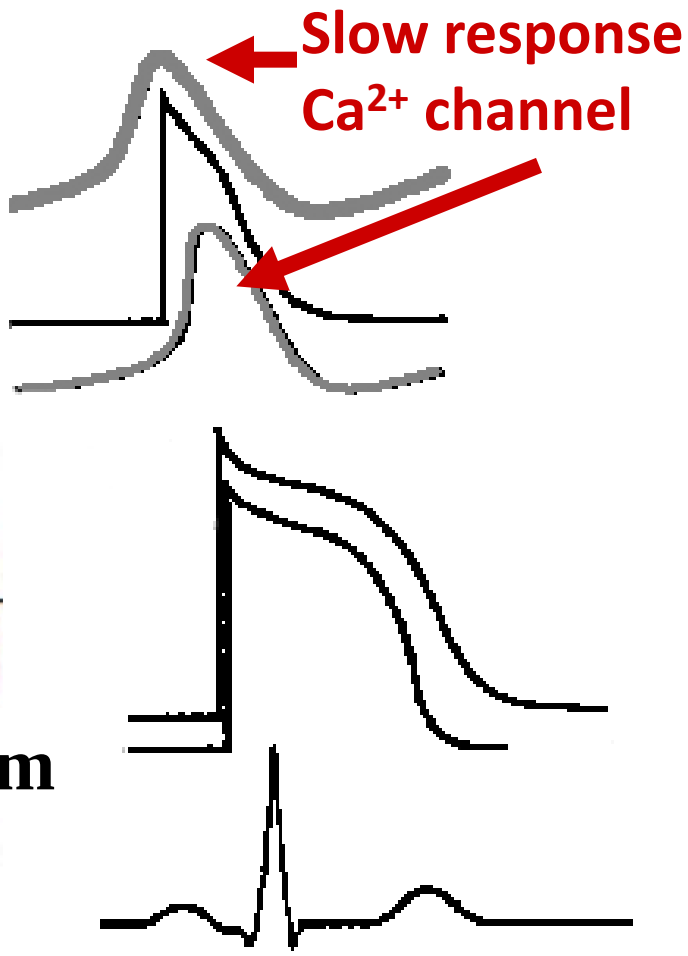
Constant perfusion pressure



SG-75
Nicorandil

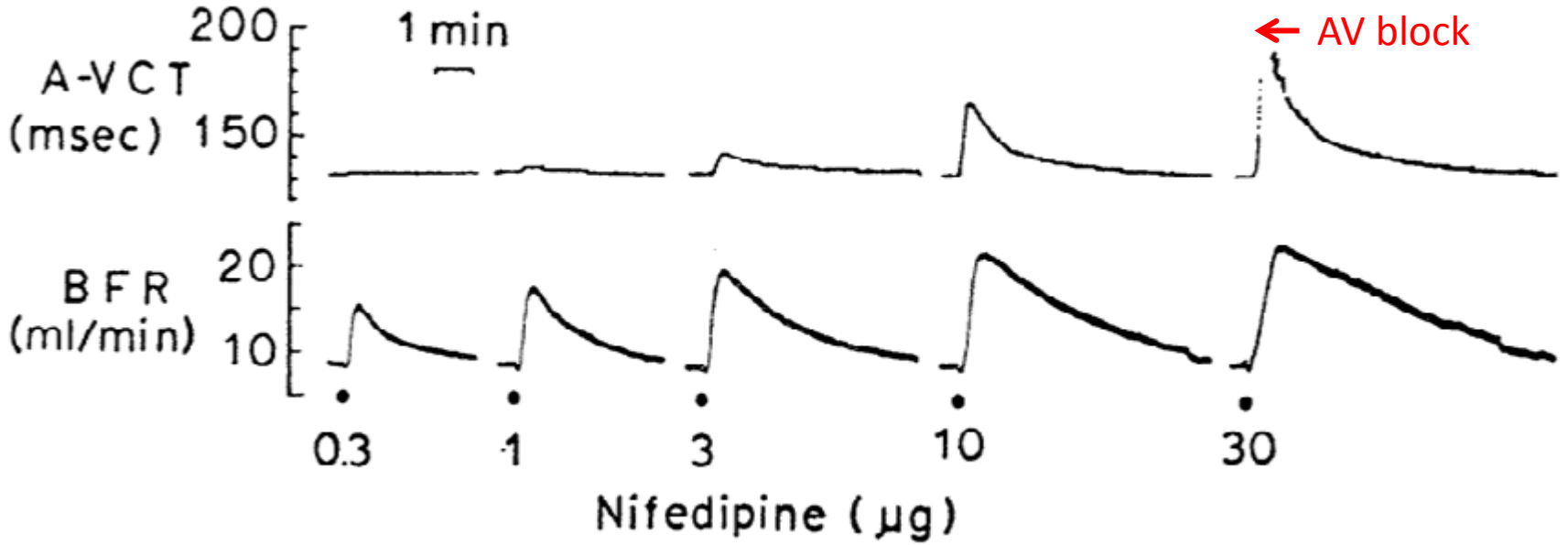
Conduction system



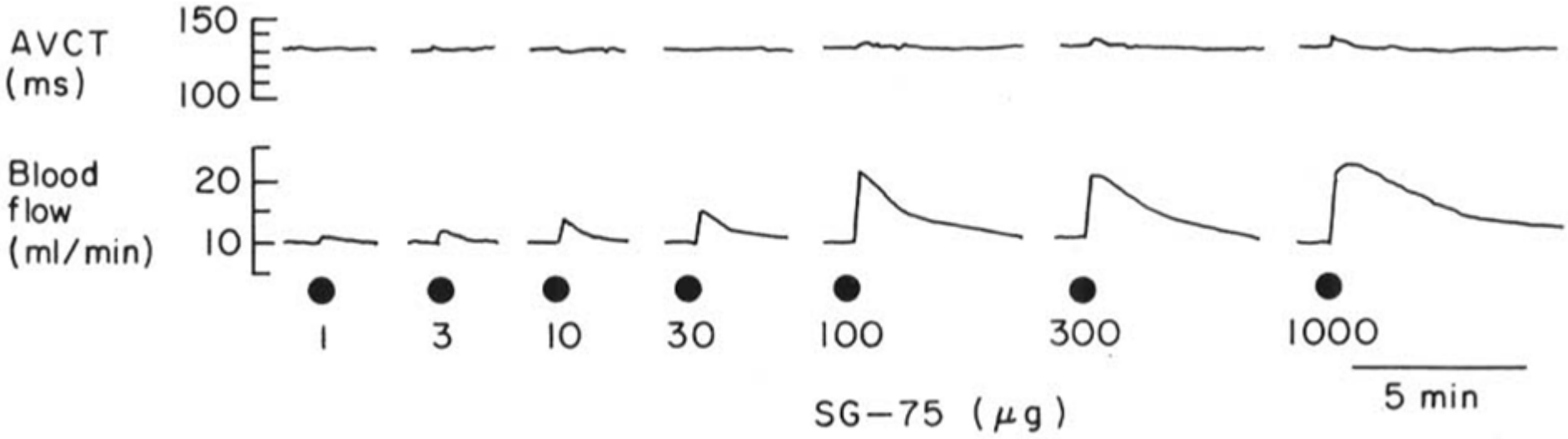


AV node; PSA: posterior septal artery←circumflexus artery
Ventricle; ASA: anterior septal artery←left coronary artery

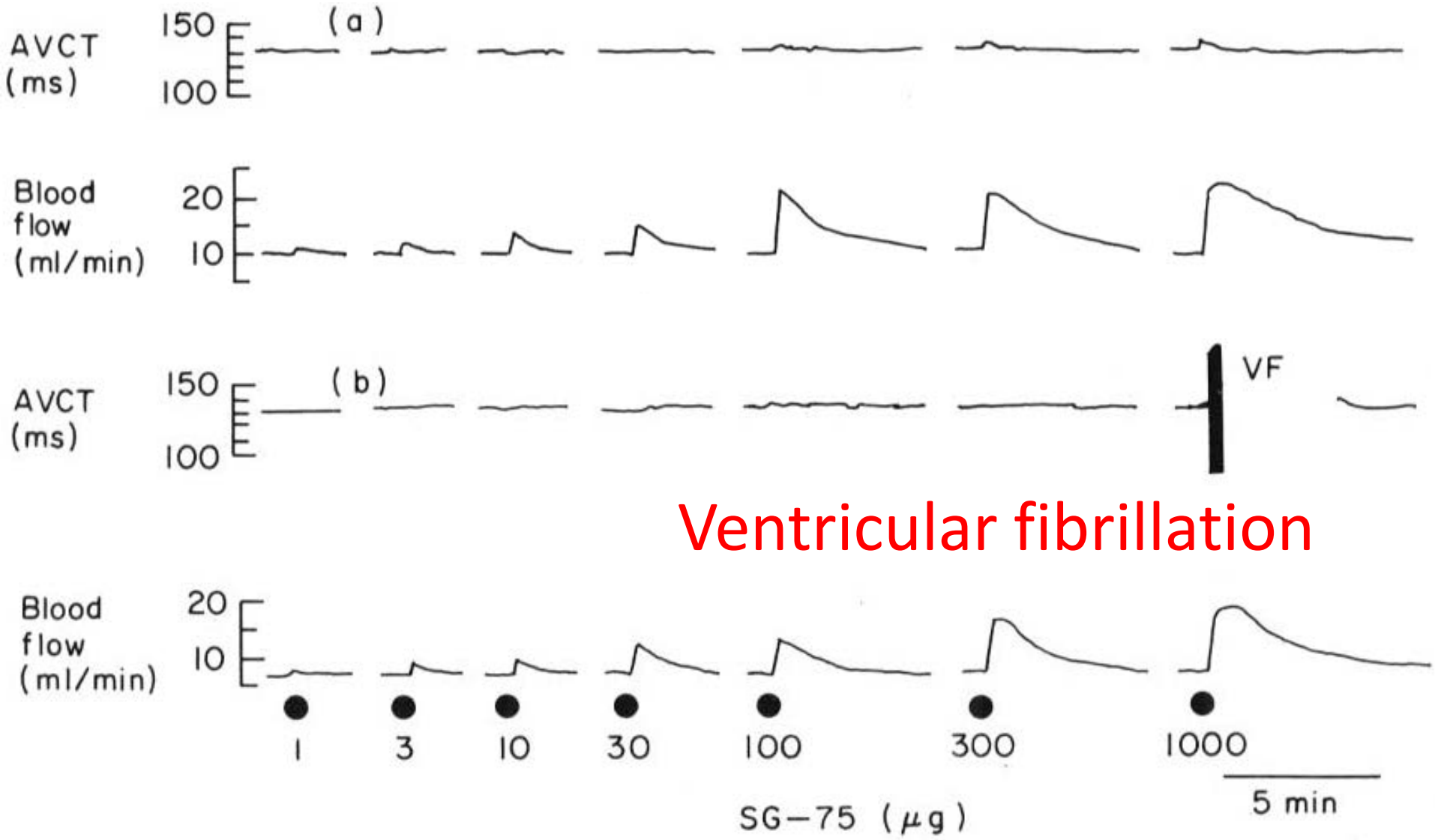
Nifedipine vs. nicorandil on AV conduction time



N-Sch. Arch. Pharmacol. 1975:290:107-12.



No effect on AV conduction, furthermore



Ventricular fibrillation

Japan. J. Pharmacol. **29**, 687–694 (1979)

CIRCUMSTANTIAL EVIDENCE FOR INCREASED POTASSIUM CONDUCTANCE OF MEMBRANE OF CARDIAC MUSCLE BY 2-NICOTINAMIDOETHYL NITRATE (SG-75)

Teruyuki YANAGISAWA, Keisuke SATOH and Norio TAIRA

Department of Pharmacology, Tohoku University School of Medicine, Sendai 980, Japan

Accepted April 19, 1979

Abstract—The mechanism of action of 2-nicotinamidoethyl nitrate (SG-75), was investigated by the use of arterially blood-perfused papillary muscle preparations of the dog. All drugs were administered intra-arterially. SG-75 shortened the effective refractory period (ERP) and decreased the rate of automaticity and developed tension of the papillary muscle, whereas verapamil failed to change the ERP despite a decrease in the developed tension. SG-75 in extremely high doses induced ventricular fibrillation. Methacholine produced decreases in the rate of automaticity and developed tension, and the actions were abolished by atropine. The SG-75-induced decreases in two parameters were not modified by atropine. These results indicate that the cardiac action of SG-75 differs from that of calcium-antagonistic vasodilators and it is suggested that the basic mechanism of action of SG-75 involves an increase in potassium conductance in the membrane of cardiac muscle, without mediation through muscarinic receptors.

Nicorandil suppresses Purkinje rate

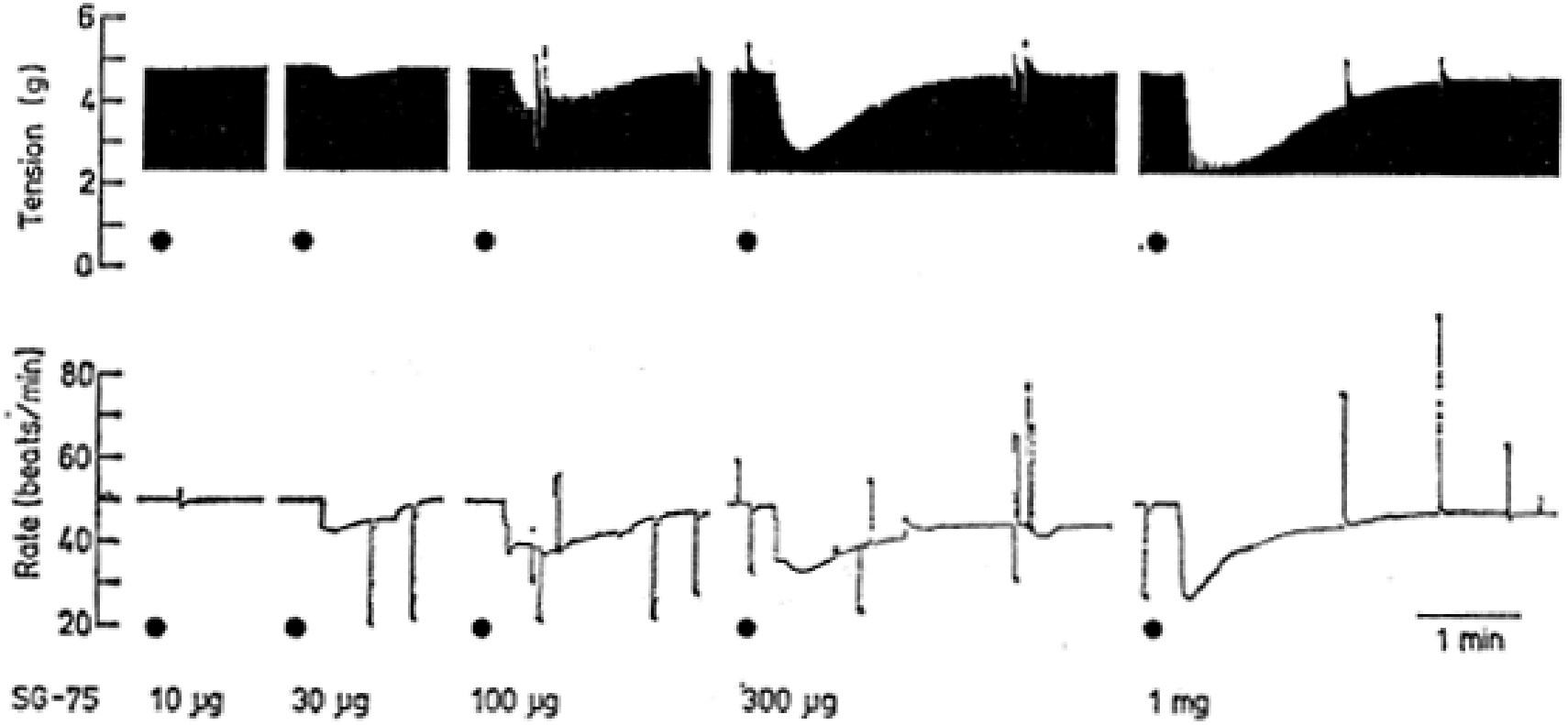


FIG. 2. Effects of SG-75 injected into the anterior septal artery on the developed tension and on the rate of automaticity of a canine blood-perfused papillary muscle.

Nicorandil 1mg, i.a.

Extra. potential

Fc

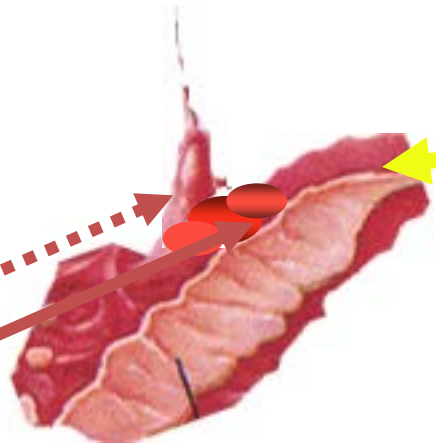
10 mV

1 g

50 ms

Blood-perfused papillary muscle

Force of contraction



Arterial blood

Extra. potential

Nicorandil

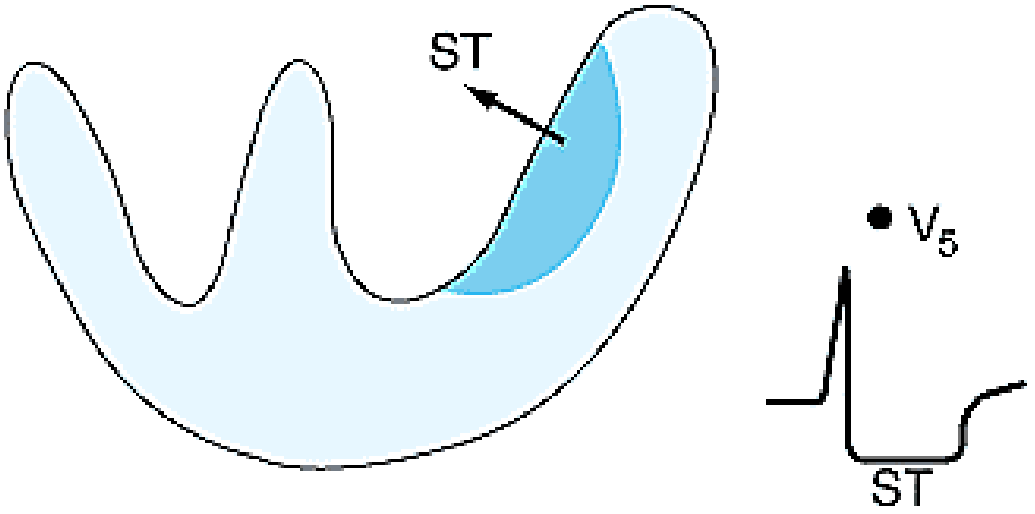
Acute ischemia causes a so-called current of injury????

The concept of K_{ATP} channel opening in ischemic/hypoxic cells.

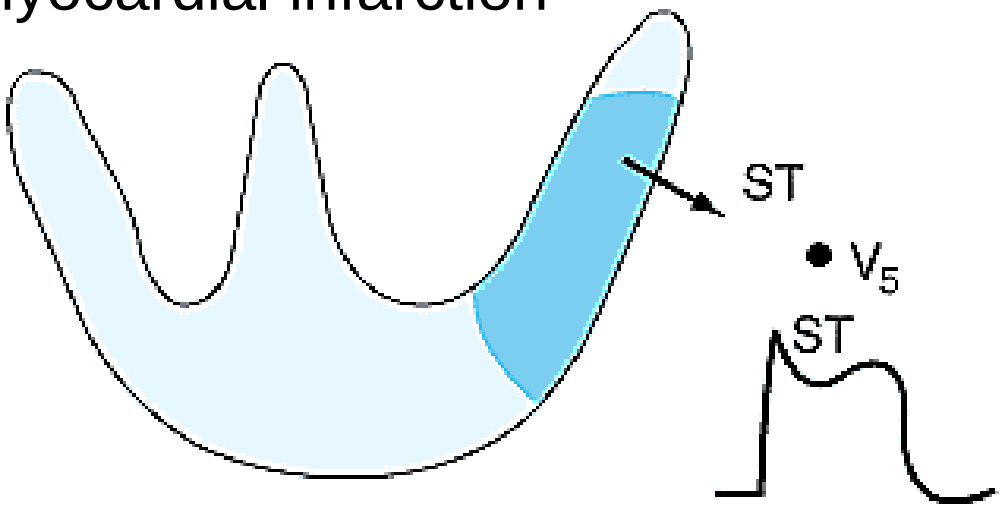
The effect of on APD of cardiac muscle.
（Ischemia-induced arrhythmia）
(Intra-arterial nicorandil-induced V.F.)

Acute ischemia causes a current of injury

Effort angina
predominant
subendocardial
ischemia

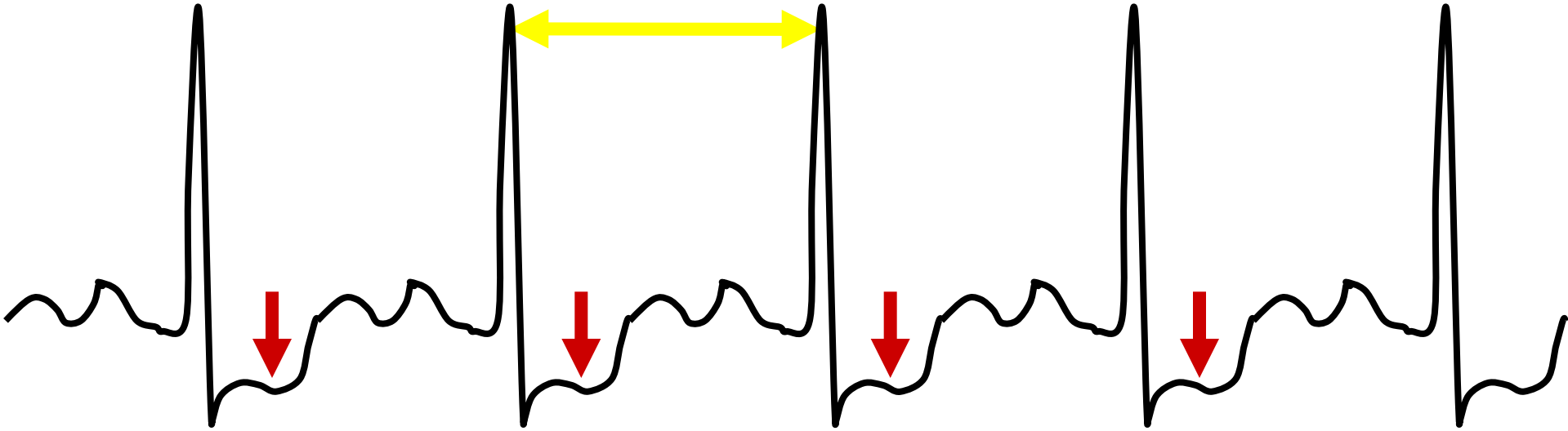


Vasospastic angina, acute myocardial infarction
ischemia involving the outer
ventricular layer (transmural
or epicardial injury)

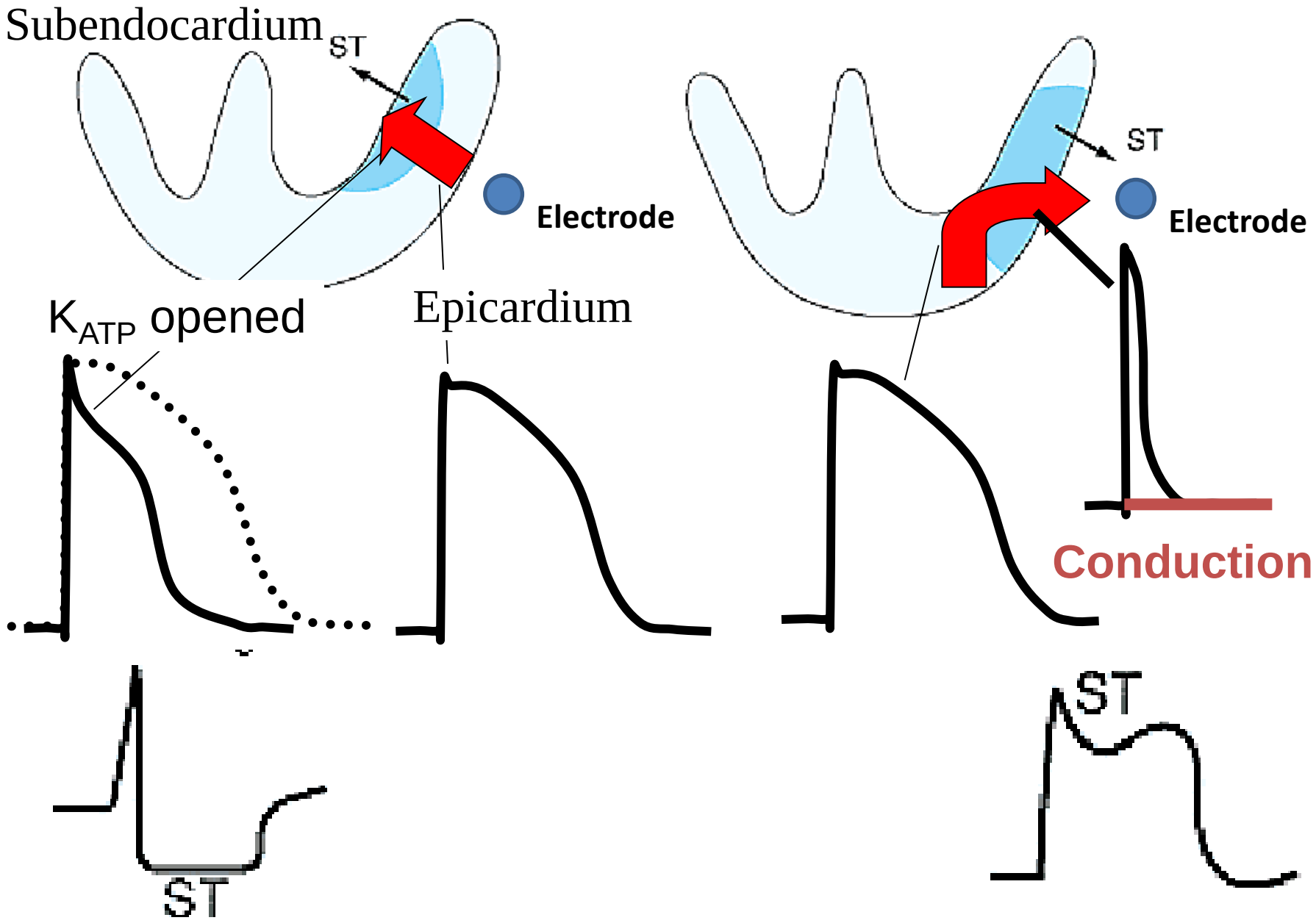


Lead V4 **at rest** (*top*) and after 4.5 min of **exercise** (*bottom*).

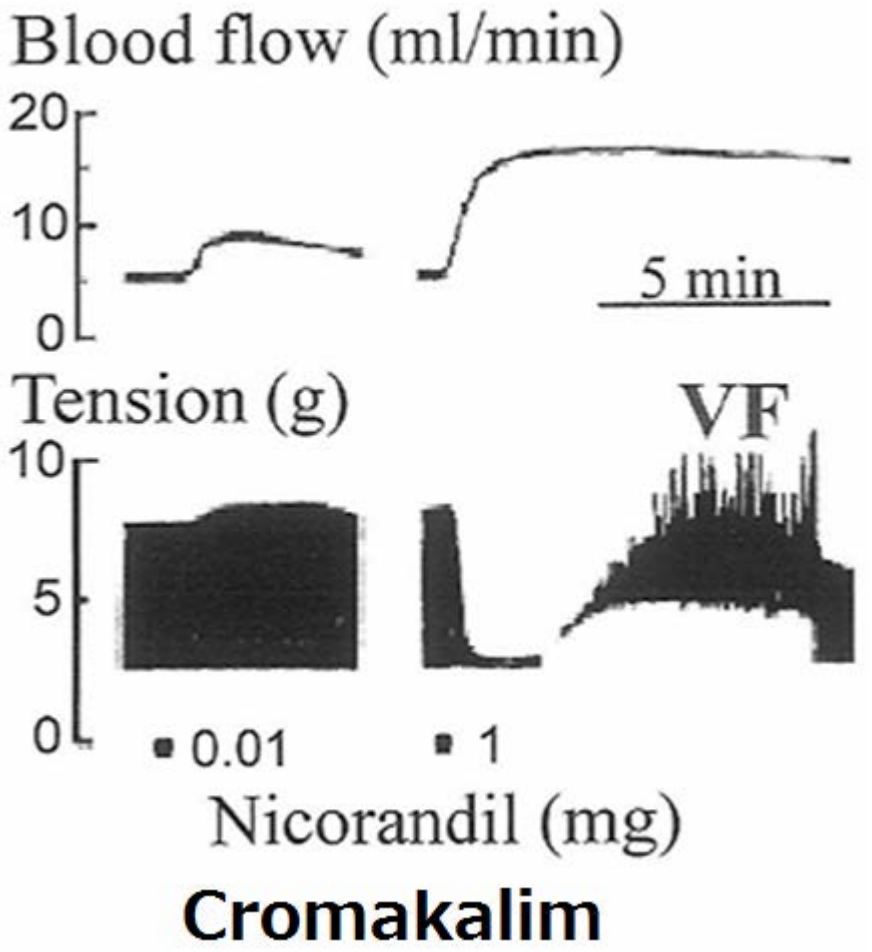
There is 0.3 mV of horizontal ST-segment depression, indicating a positive test for ischemia.

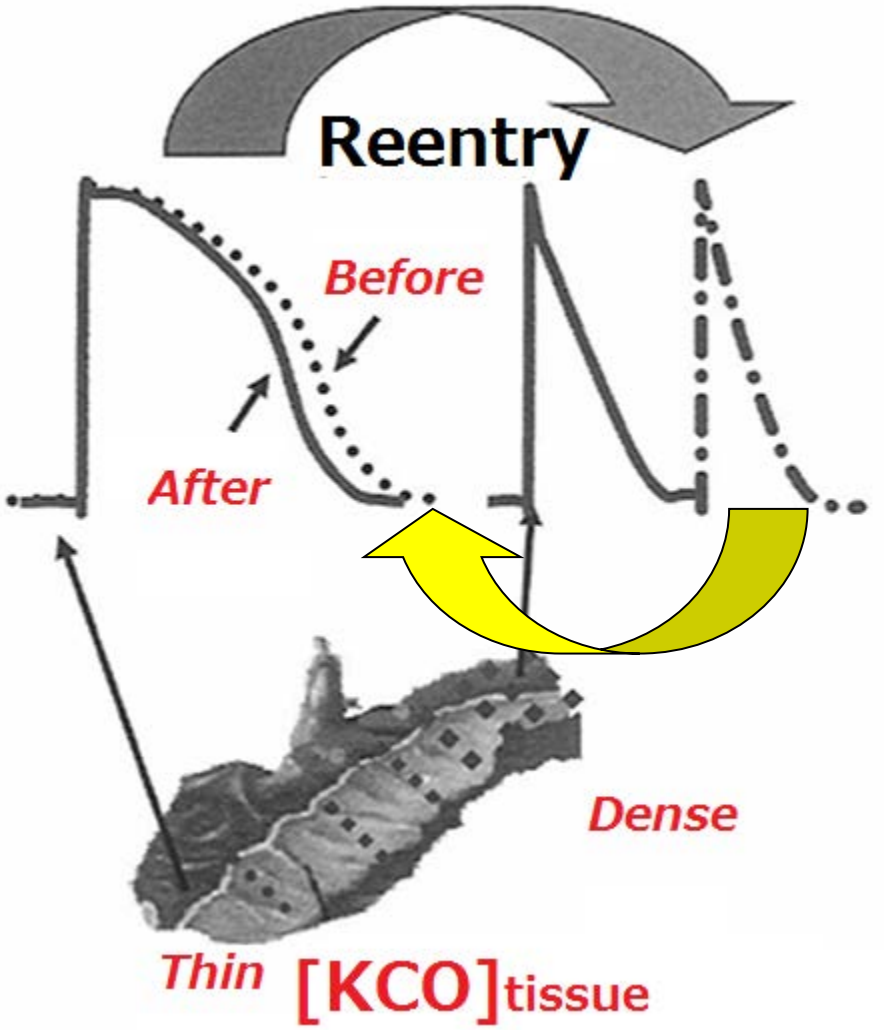


Acute ischemia causes ST changes



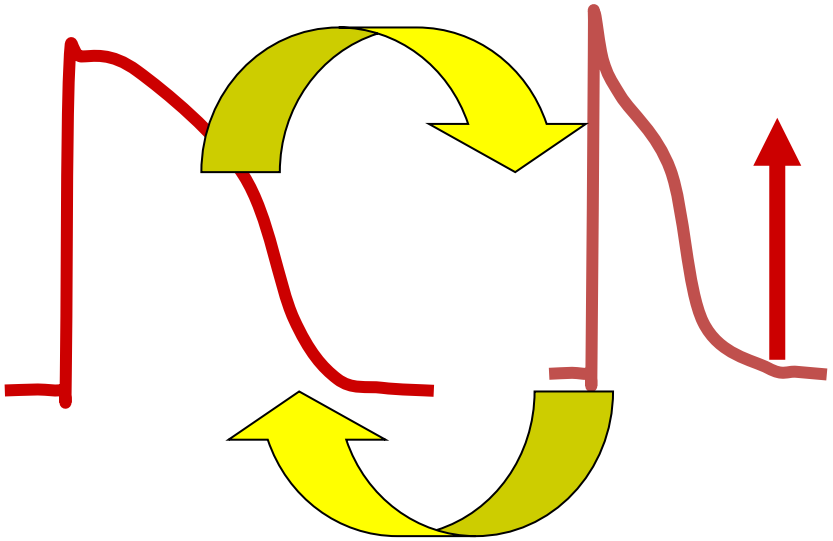
Ischemic arrhythmias in the light of K_{ATP}
Reentry→VT, VF

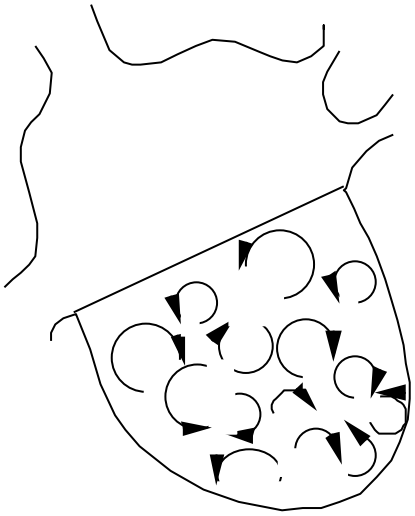




http://ir.library.tohoku.ac.jp/re/bitstream/10097/40205/1/YANAGISAWA-Teruyuki-01-09-0012.pdf

SG-75-induced VT & VF in experiments with blood-perfused canine preparations





We have given clinicians the caution of the risk of **intracoronary administration** of nicorandil.

Fortunately, there has been no report related accidents

Nicorandil as a Hybrid Between Nitrates and Potassium Channel Activators

Norio Taira, MD

(Am J Cardiol 1989;63:18J-24J)

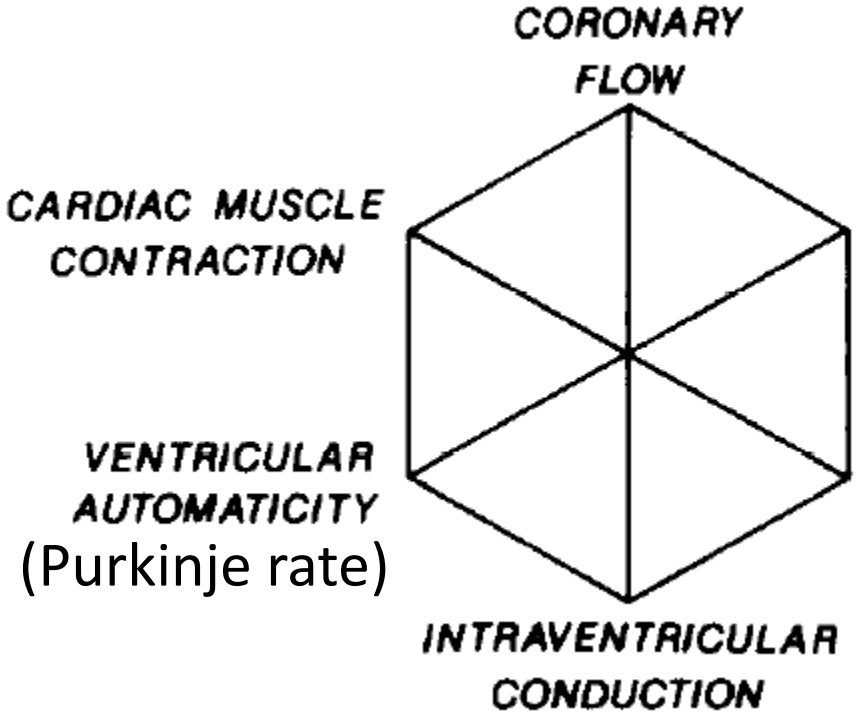
・Cromakalim and pinacidil, nonnitrate KCO, have essentially the same cardiovascular profile as nicorandil in isolated, blood-perfused canine heart preparations.

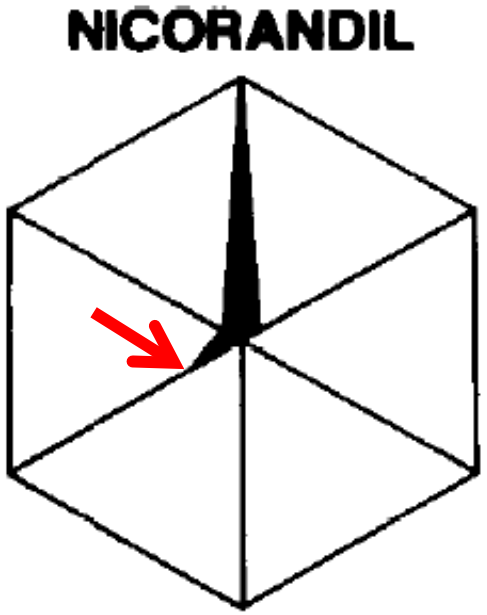
1) The property of nicorandil as a resistive vessel dilator highly selective for vasculature originates in its mechanism of action as a K-channel activator.

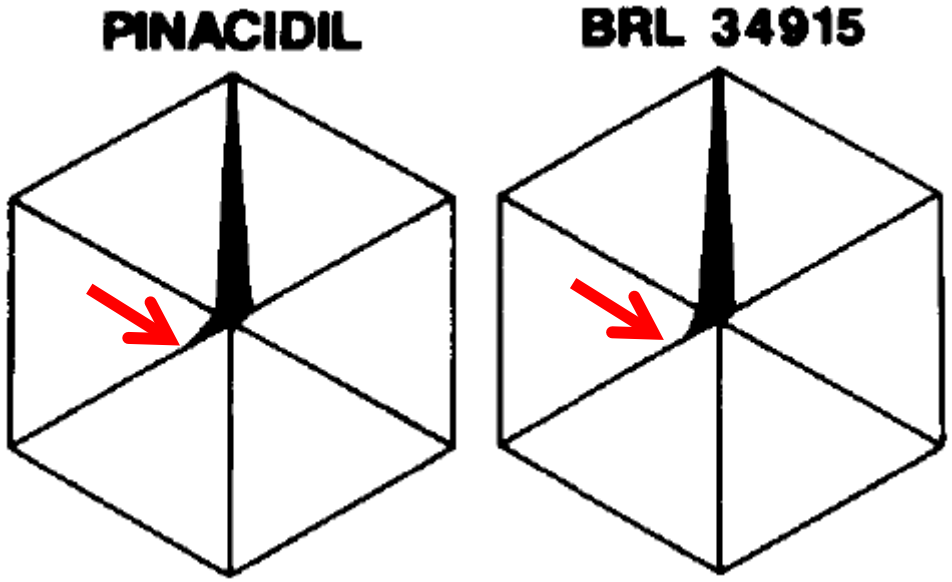
2) The non-unanimous effect of nicorandil on venous return is a result of the opposing actions as a capacitive (action as a nitrate) and a resistive vessel dilator.

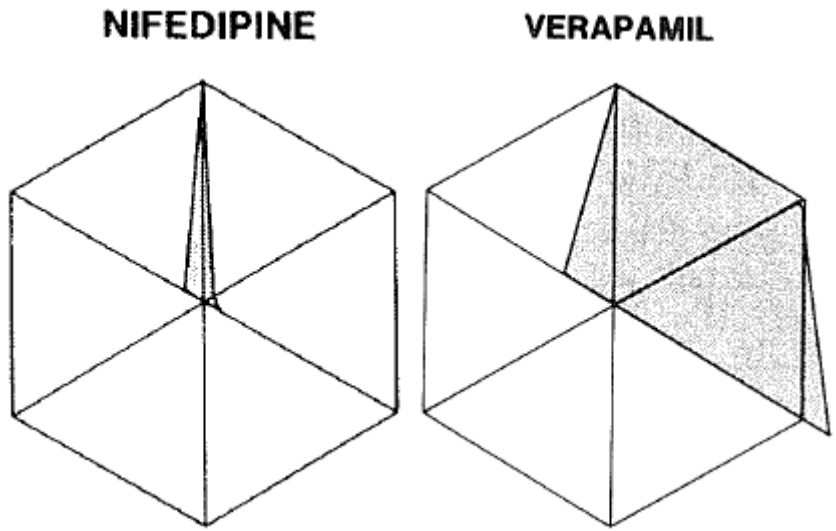
3) Nicorandil, with its hybrid nature, is advantageous over specific K-channel activators and classic nitrates in therapeutic implications.

Selectivity spectra for coronary blood flow vs. cardiac variables



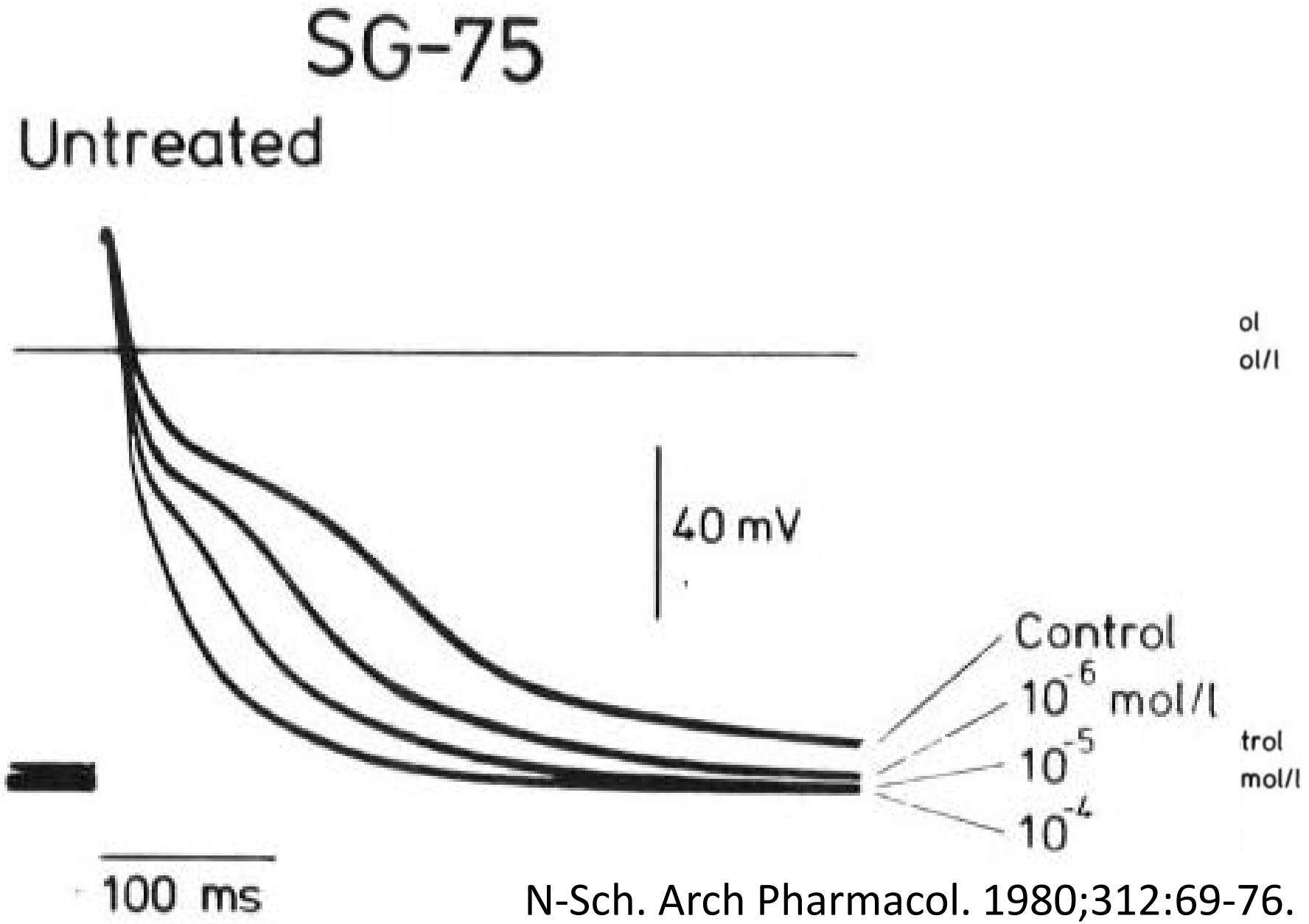






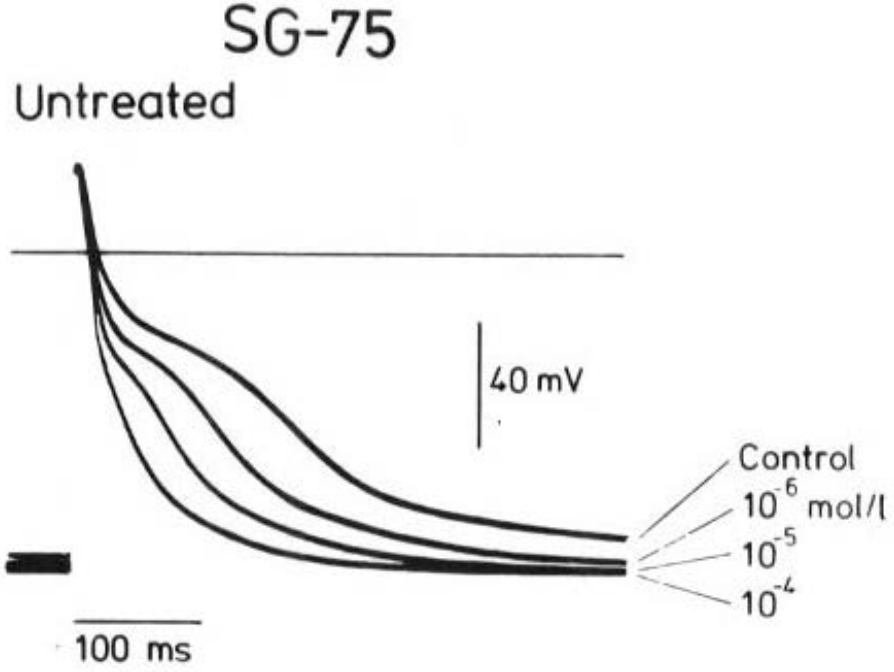
Am J Cardiol. 1987;59(3):24B-29B

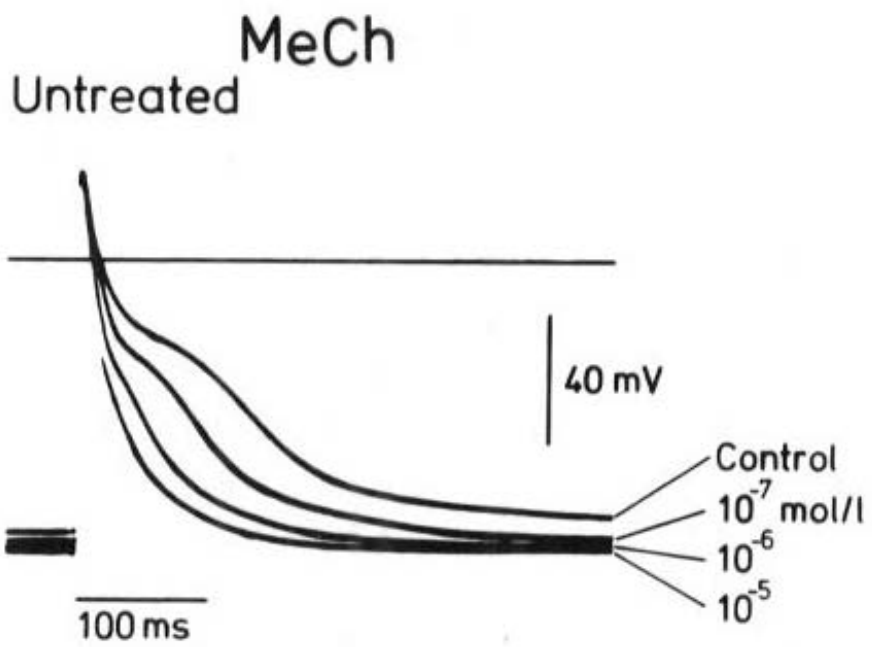
Canine atrial muscle comparison with ACh

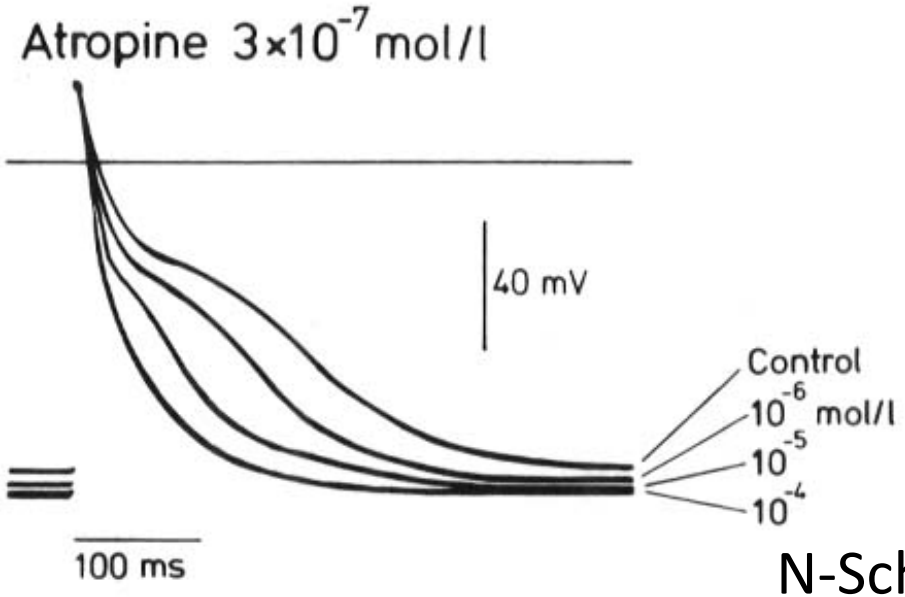


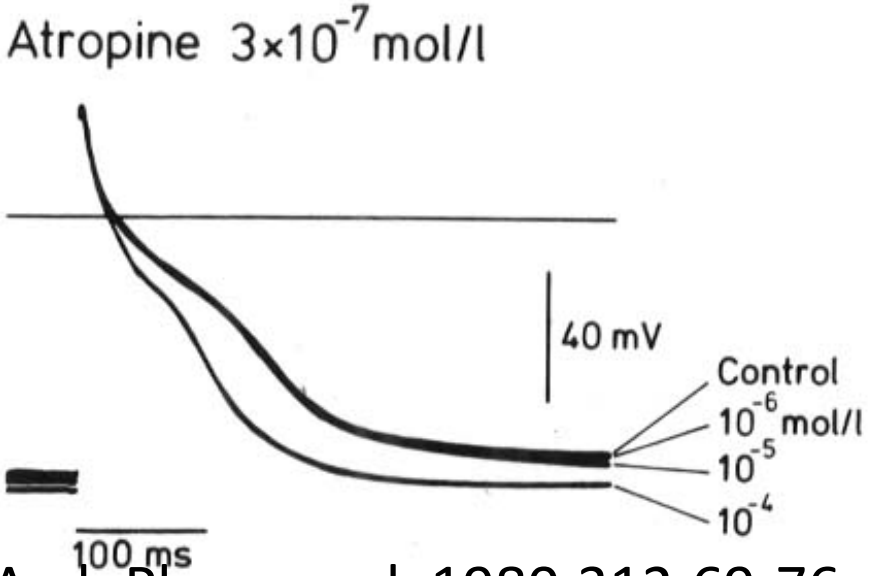
N-Sch. Arch Pharmacol. 1980;312:69-76.

Canine atrial muscle comparison with ACh



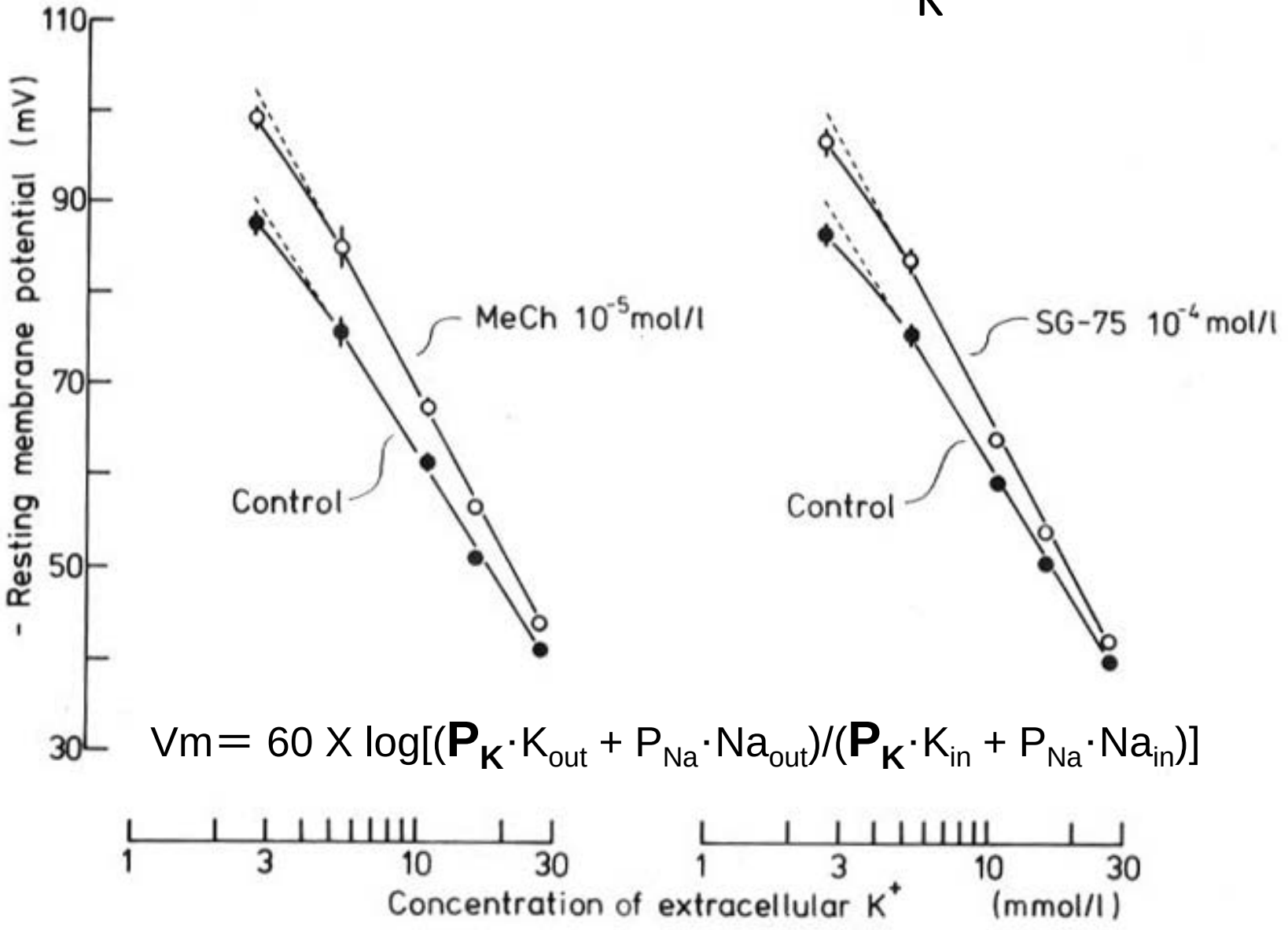






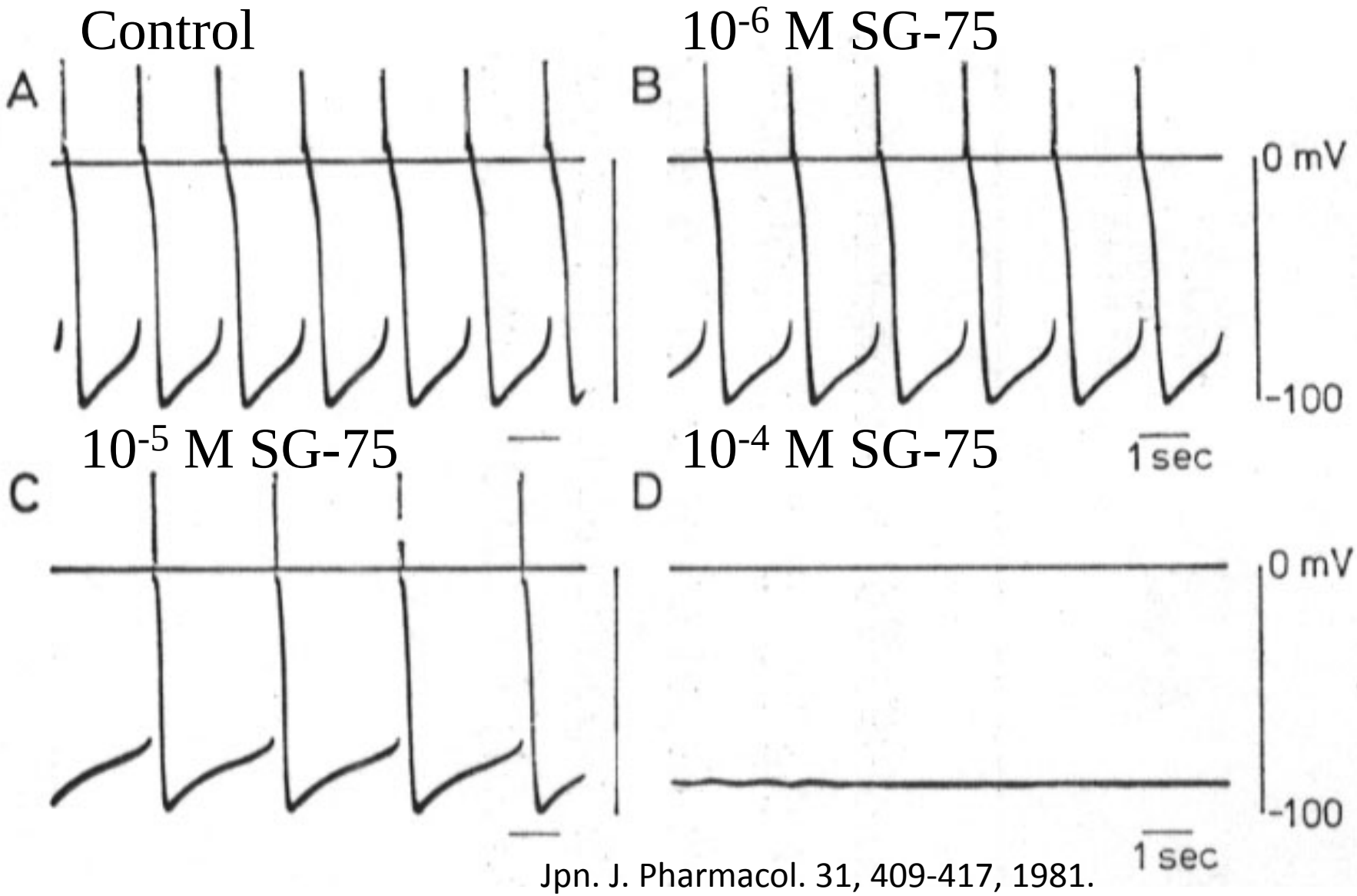
N-Sch. Arch Pharmacol. 1980;312:69-76.

SG-75 increases P_K



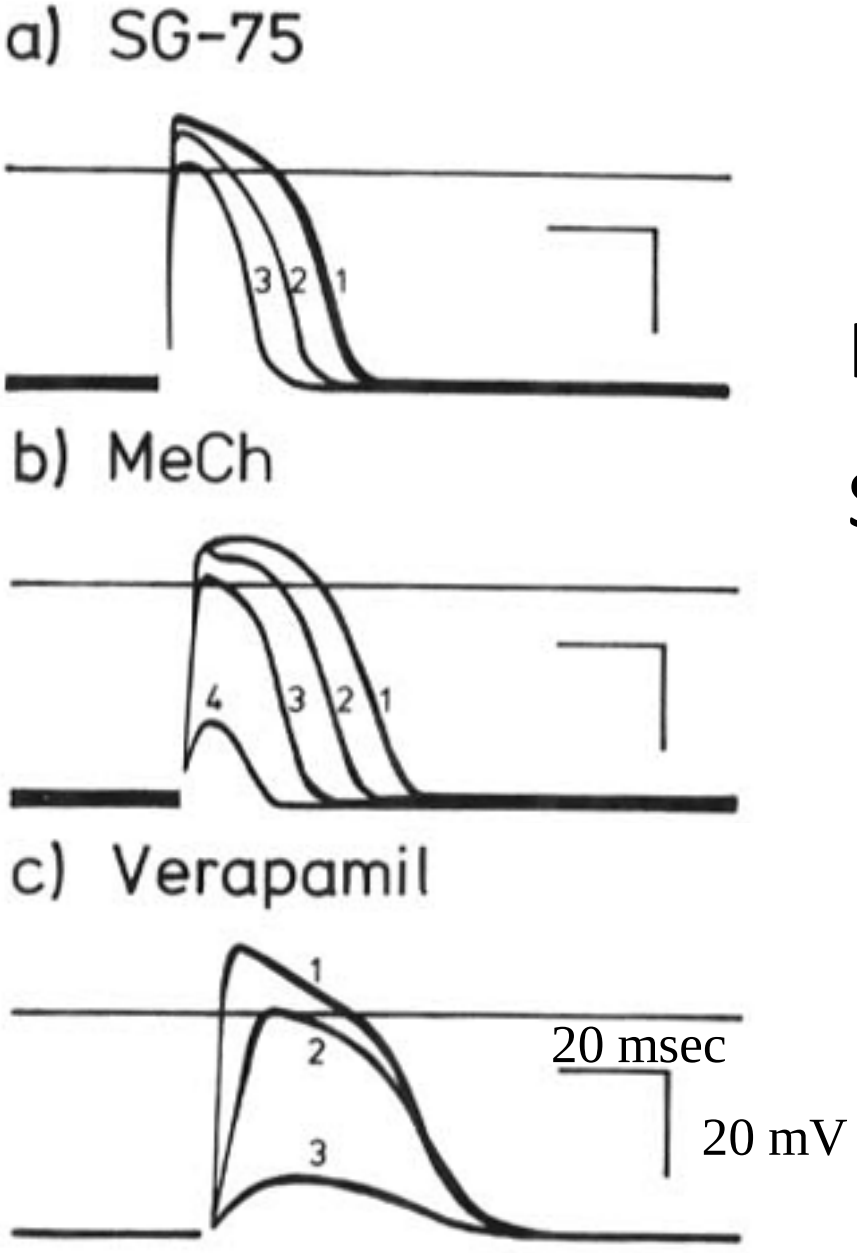
$$Vm = 60 \times \log[(\mathbf{P_K} \cdot K_{out} + P_{Na} \cdot Na_{out})/(\mathbf{P_K} \cdot K_{in} + P_{Na} \cdot Na_{in})]$$

Effect of SG-75 on membrane potentials of a spontaneously firing canine Purkinje fiber



Jpn. J. Pharmacol. 31, 409-417, 1981.

Slow response in 27 mM K^+



Hyperpolarization

Shorten APD

【Conclusion-1】

Findings in blood-perfused cardiac prep.

- **SG-75 increases coronary blood flow.**
- No effect on AV conduction
- Induction of ventricular fibrillation in high dose
- Shorten QT interval
- Shorten APD of ventricular muscle

The mechanism is not Ca^{2+} channel blockade.

K^+ channel opening.

K^+ channel openers (K_{ATP}COs)

- Historical points of view
- Why they are **not** successful for the antihypertensive agents?
- Vasospastic angina
- Hyperpolarization-relaxation coupling
- Progress of new types KCOs

Tohoku J. exp. Med., 1985, **145,** 85-90

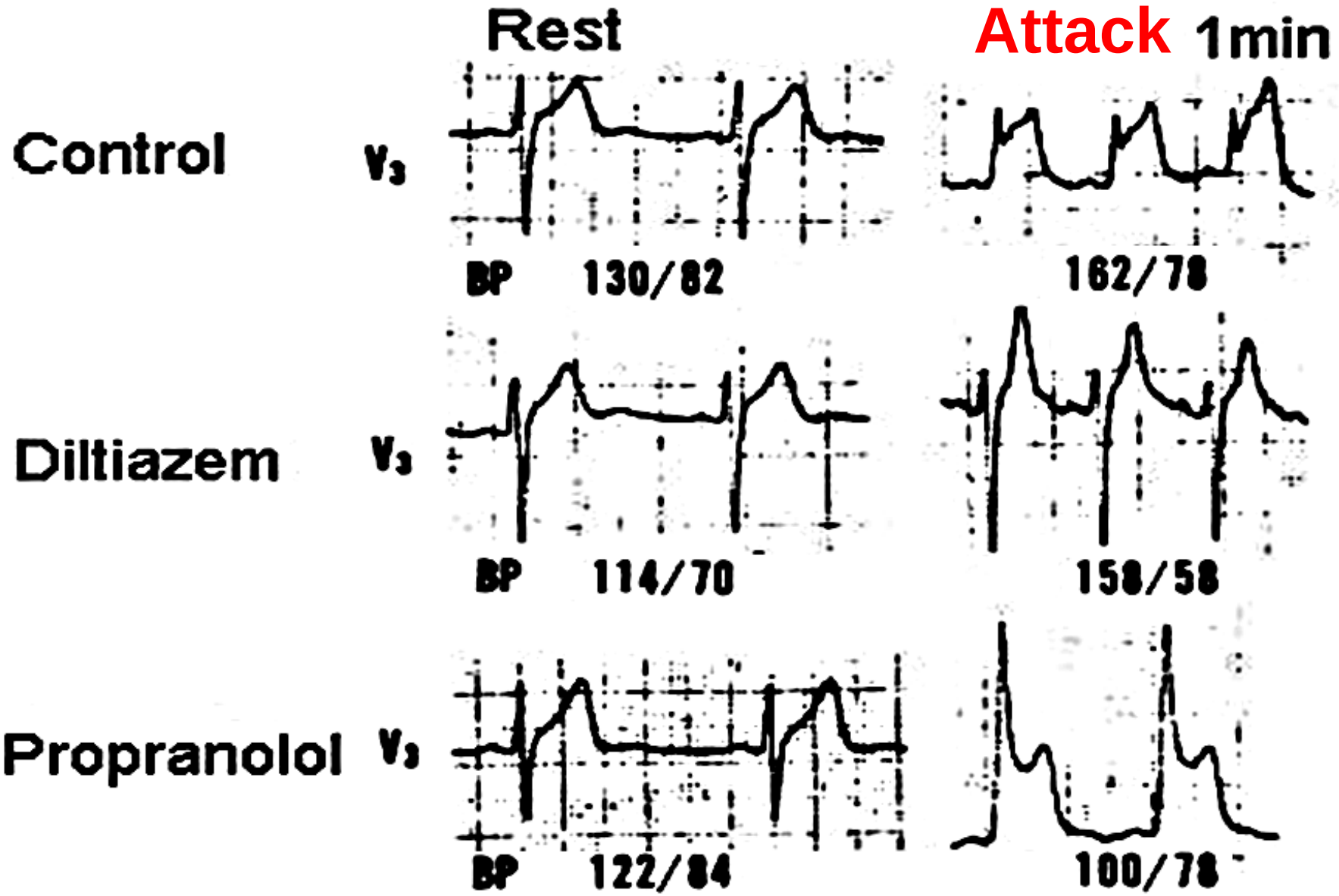
As a model of vasospastic angina

Abolition of Spontaneous Rhythmic Contractions of Isolated Monkey Coronary Arteries by Diltiazem, Nifedipine, Verapamil and Nicorandil but Not by Nitroglycerin

KUNIAKI ISHII, TERUYUKI YANAGISAWA, KEISUKE SATOH and NORIO TAIRA

Department of Pharmacology, Tohoku University School of Medicine, Sendai 980

Treatment of **vasospastic angina**



Yasue H et al. Circulation 1979;59:938-48

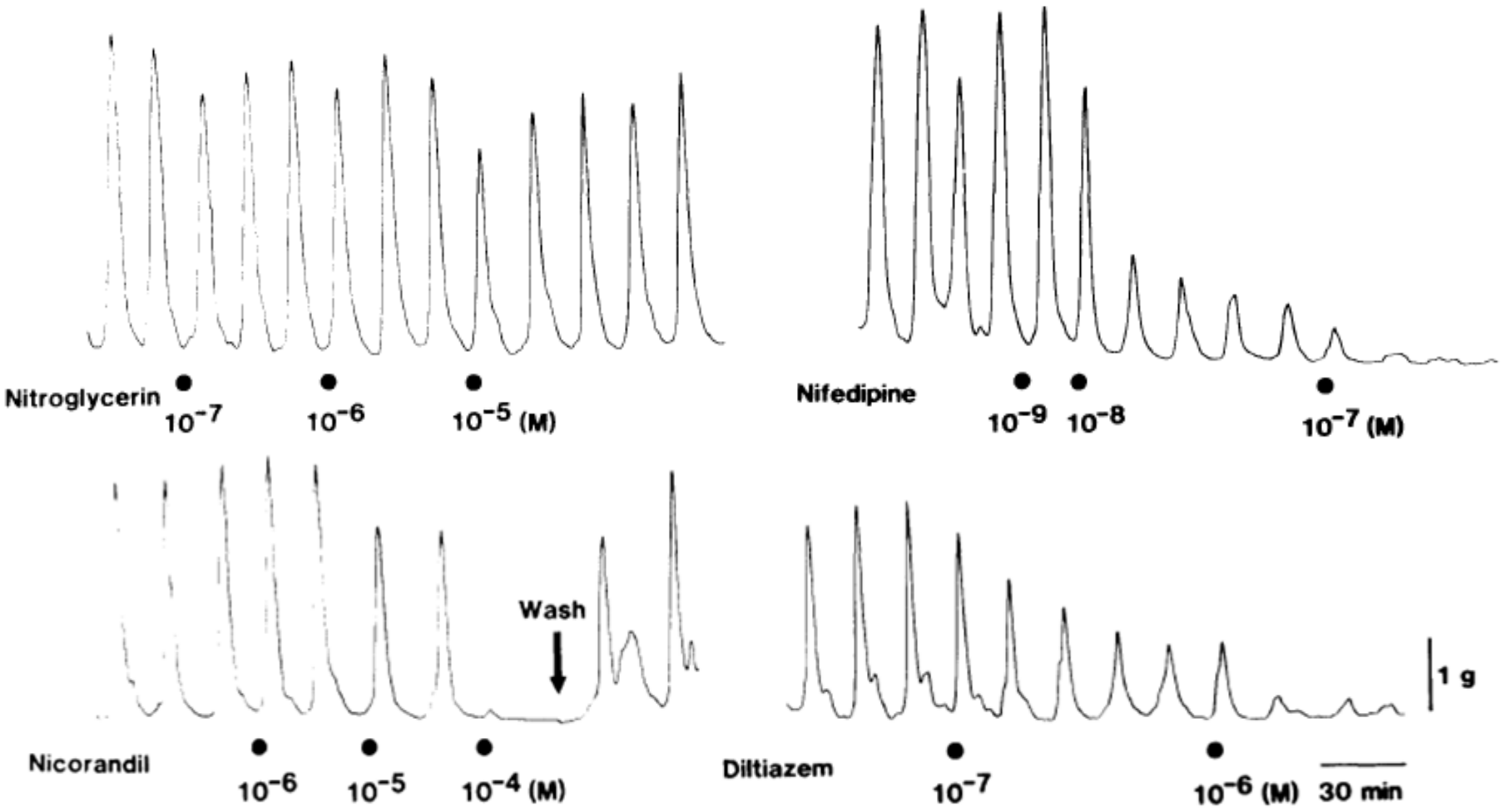
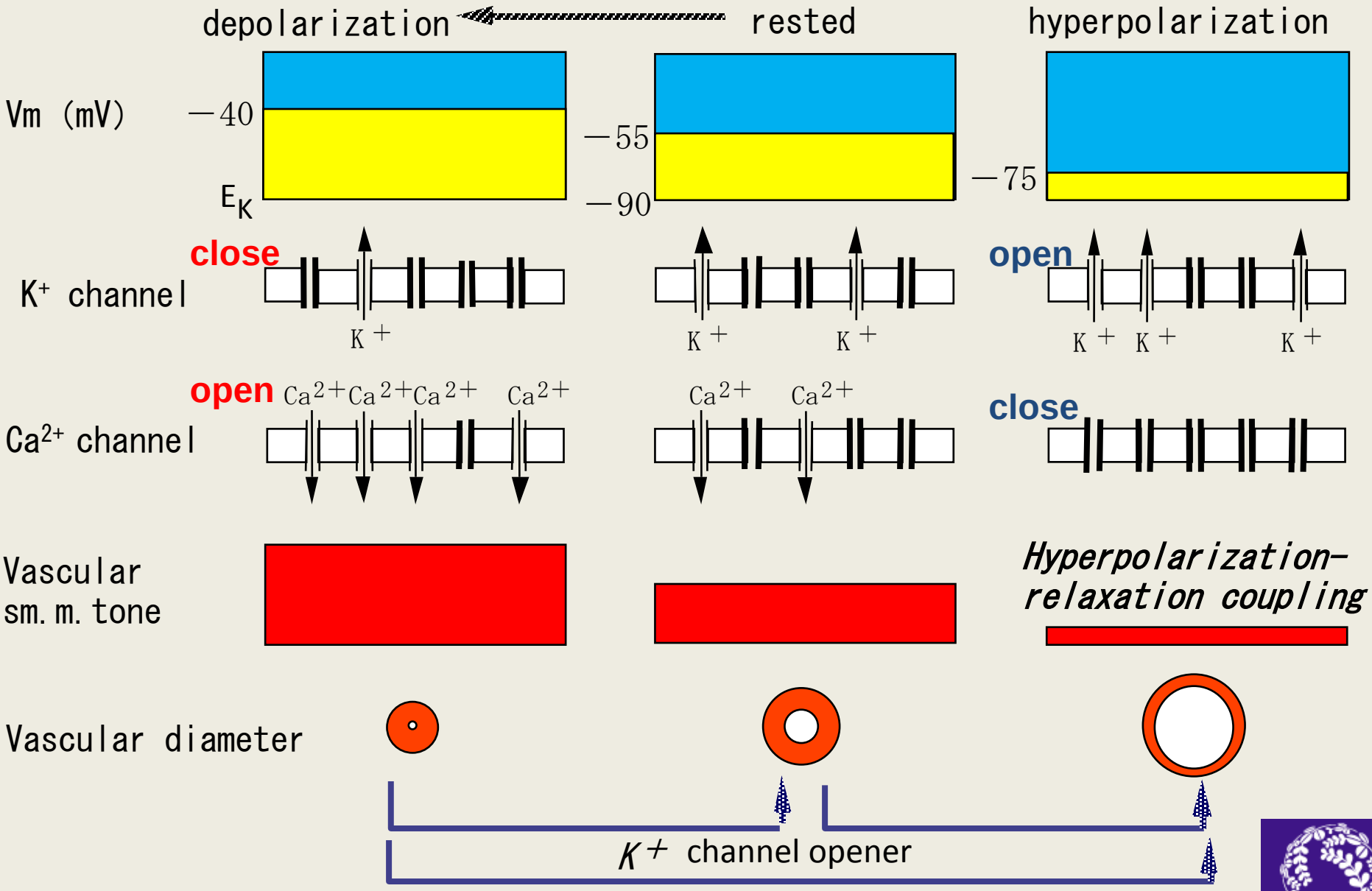


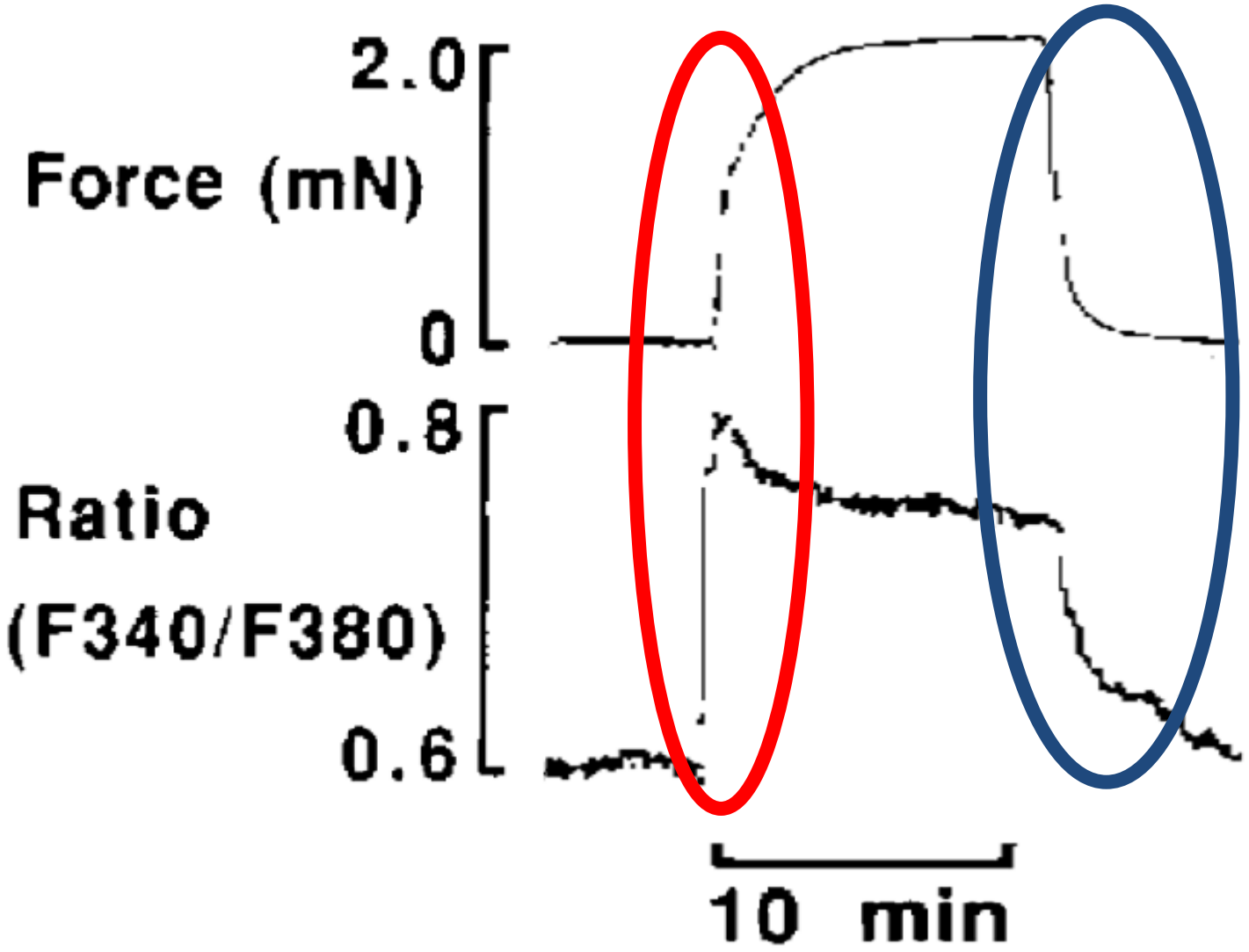
Fig. 1. Spontaneous rhythmic contractions of a coronary artery ring of the left circumflex coronary artery of a rhesus monkey and effects of vasodilators thereon.

Hypertension, spasm, agonists

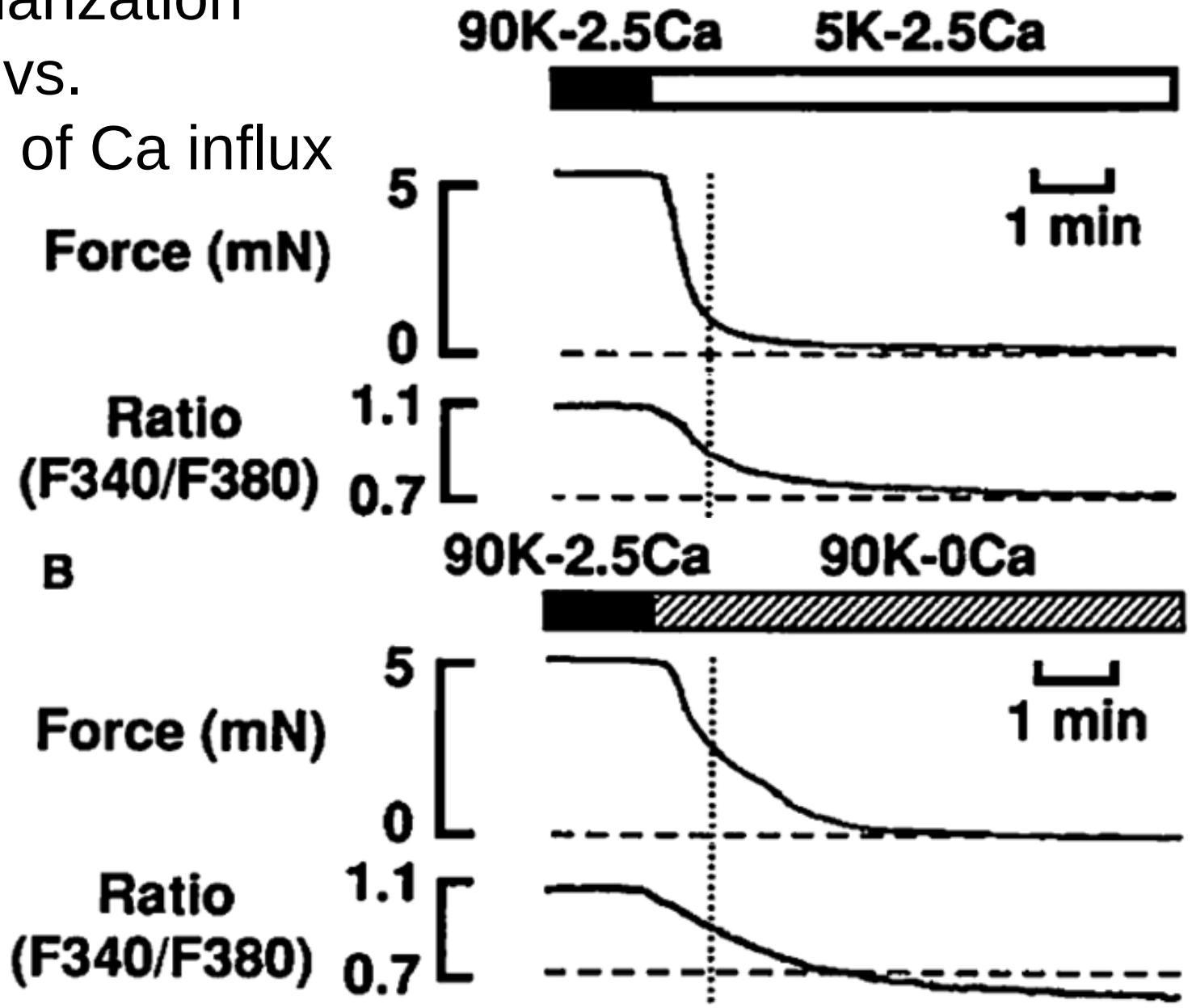


Dissociation of $[Ca^{2+}]_i$ & Force of contraction

KCl (90 mM) contraction

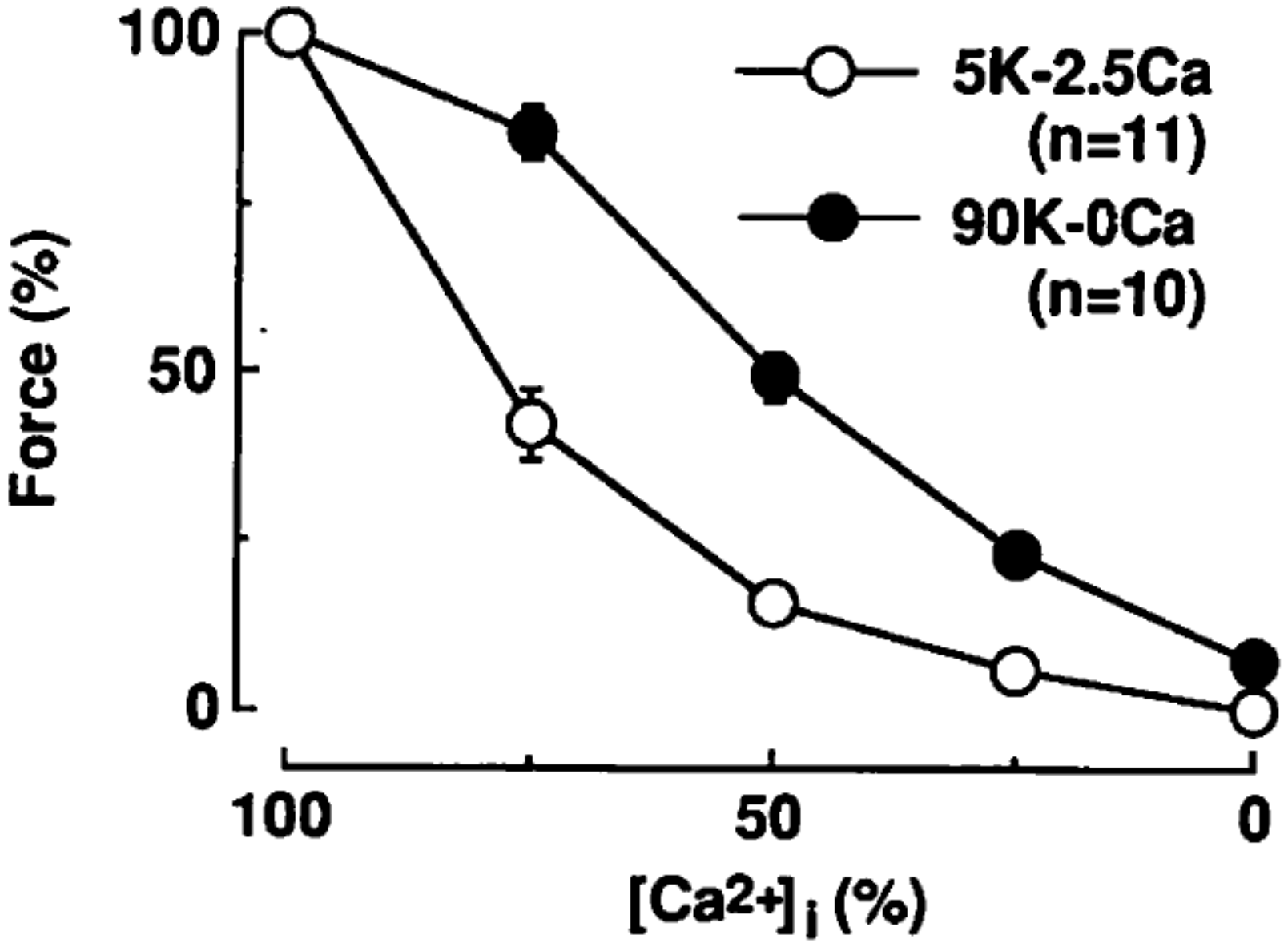


Repolarization vs. Inhibition of Ca influx

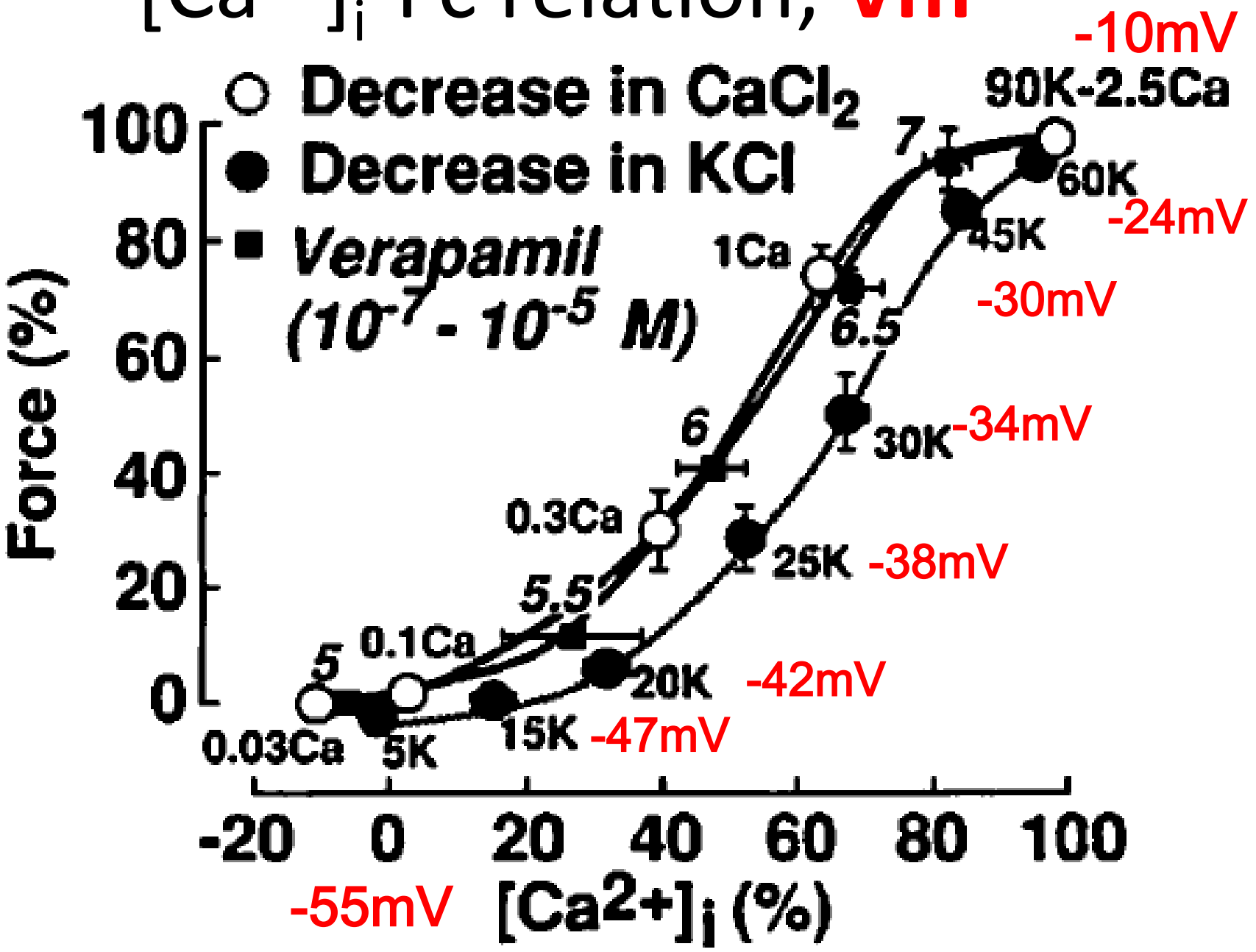


Am. J. Physiol. 1994; 267: H614-H621.

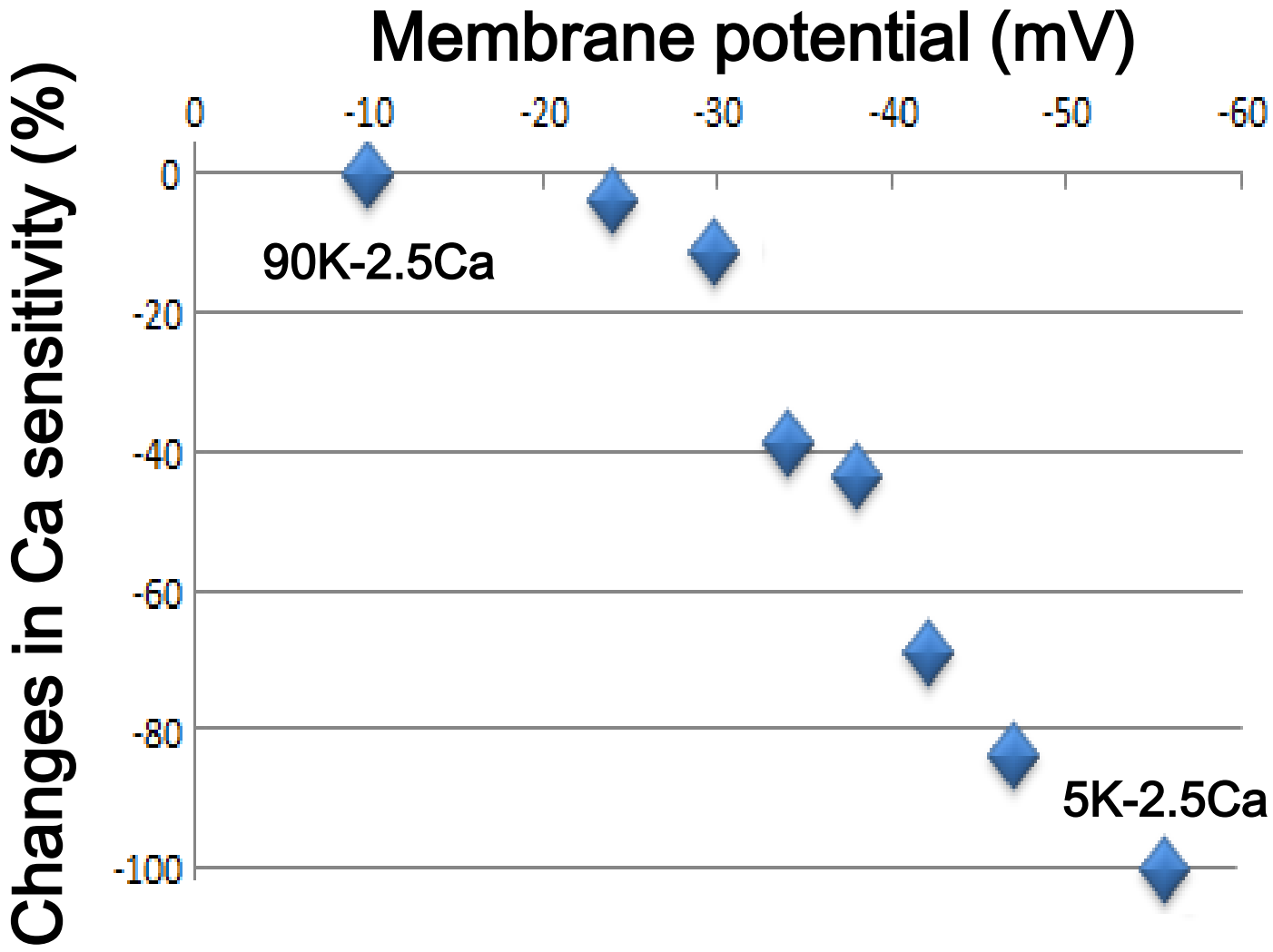
Repolarization vs. Inhibition of Ca influx



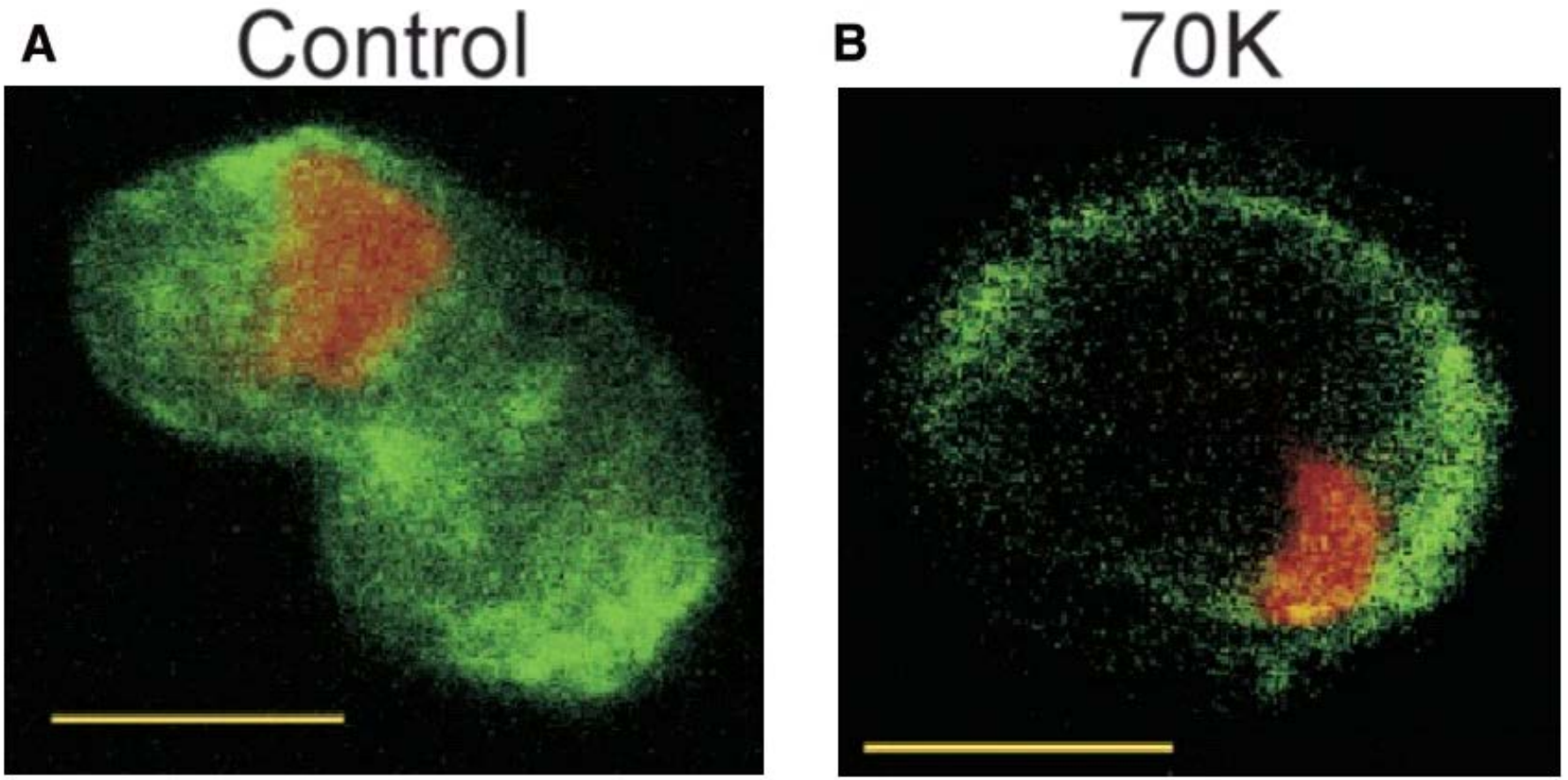
$[Ca^{2+}]_i$-Fc relation; **Vm**



Repolarization & Ca sensitivity



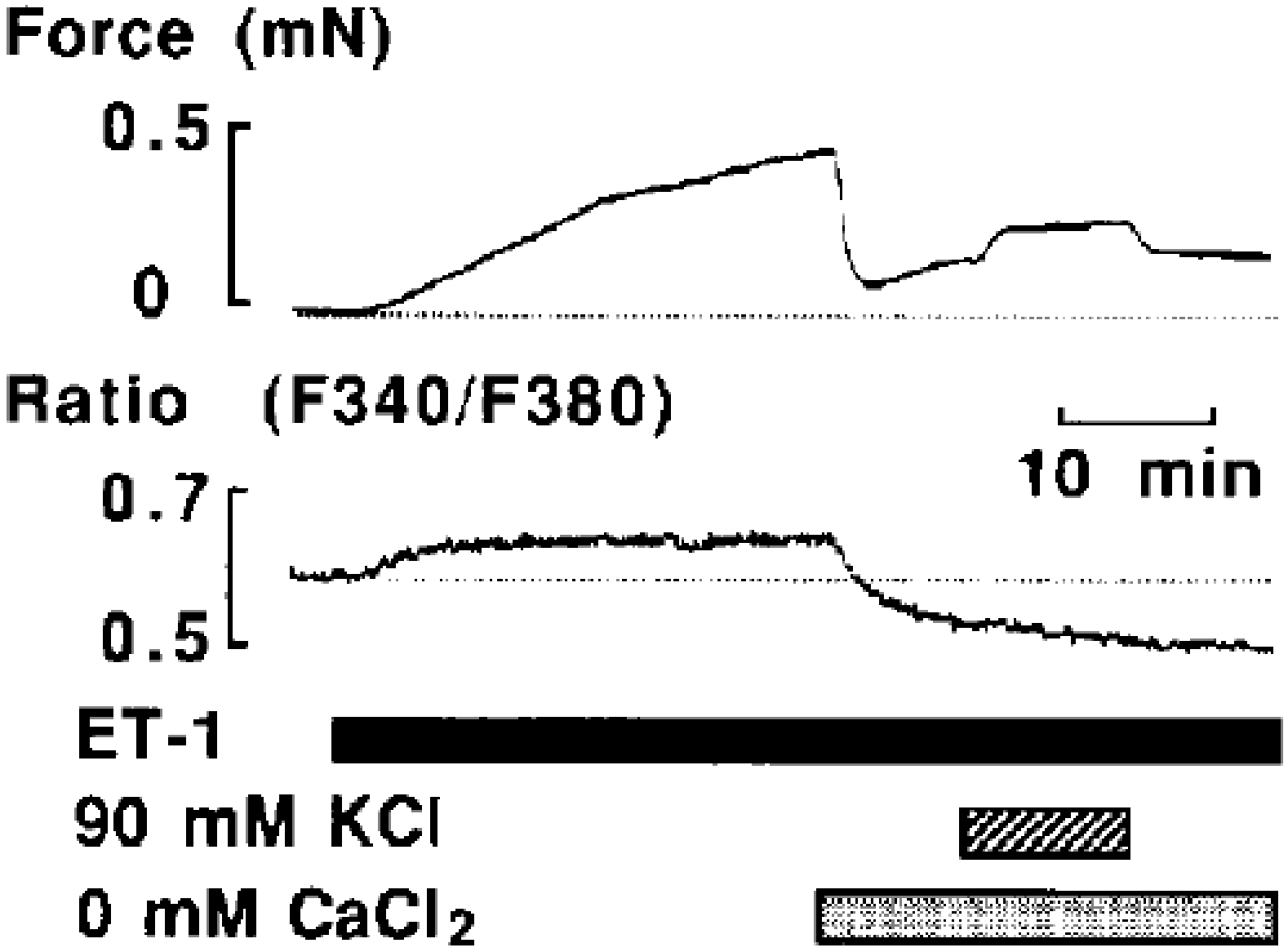
RhoK distribution



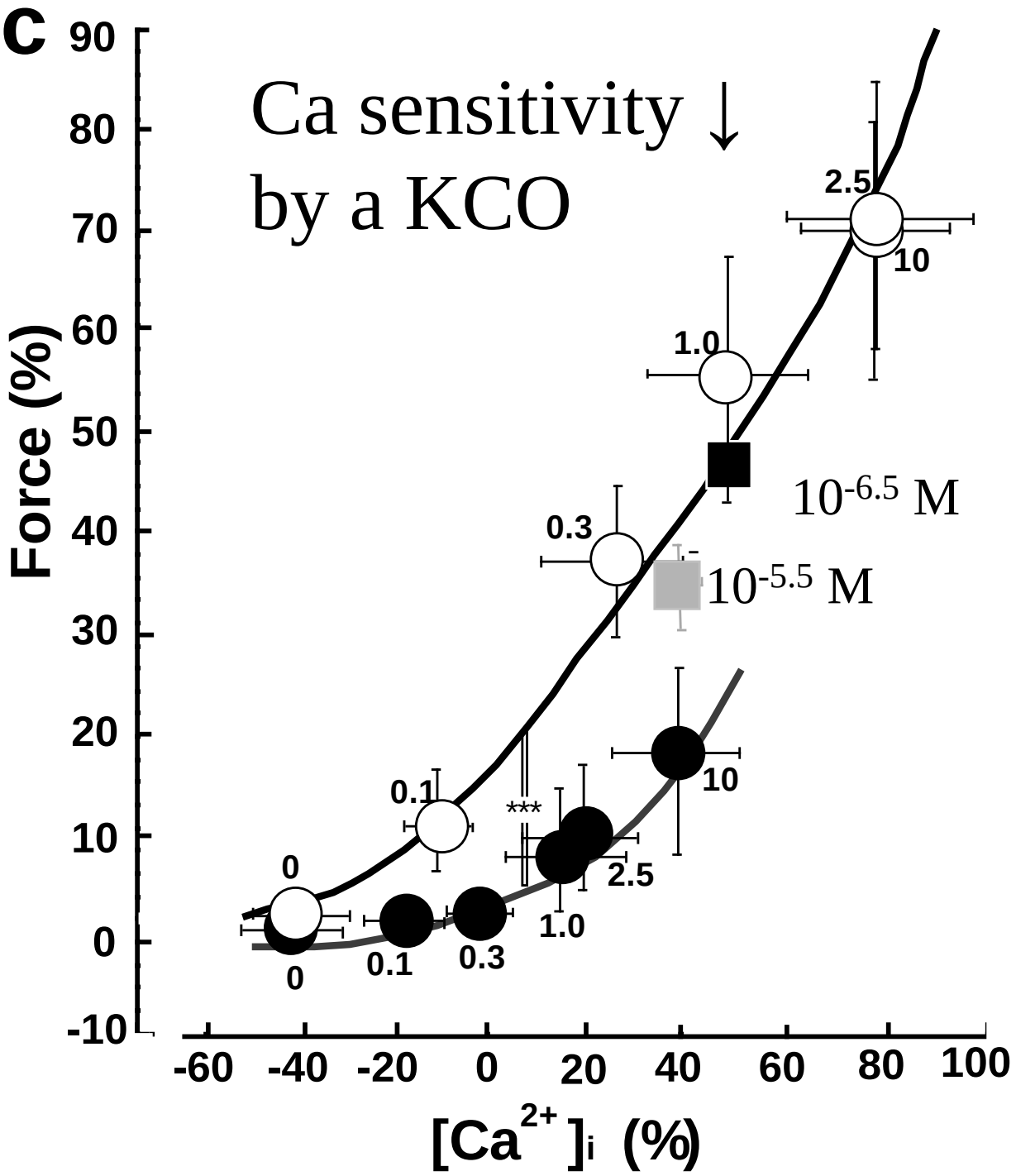
Cytosolic distribution of activated RhoA in isolated myocytes and effect of the Rho-associated kinase (ROCK) inhibitor Y27632 on 70K-induced contraction in rat basilar artery. Confocal immunofluorescent images of RhoA distribution (RhoA, green; cell nucleus, red) in a single basilar smooth muscle cell at rest (A) and after stimulation with 70K (B). Scale bars=7 μm.

Fernandez-Tenorio et al.: Circ Res 2011;108:1348-57.

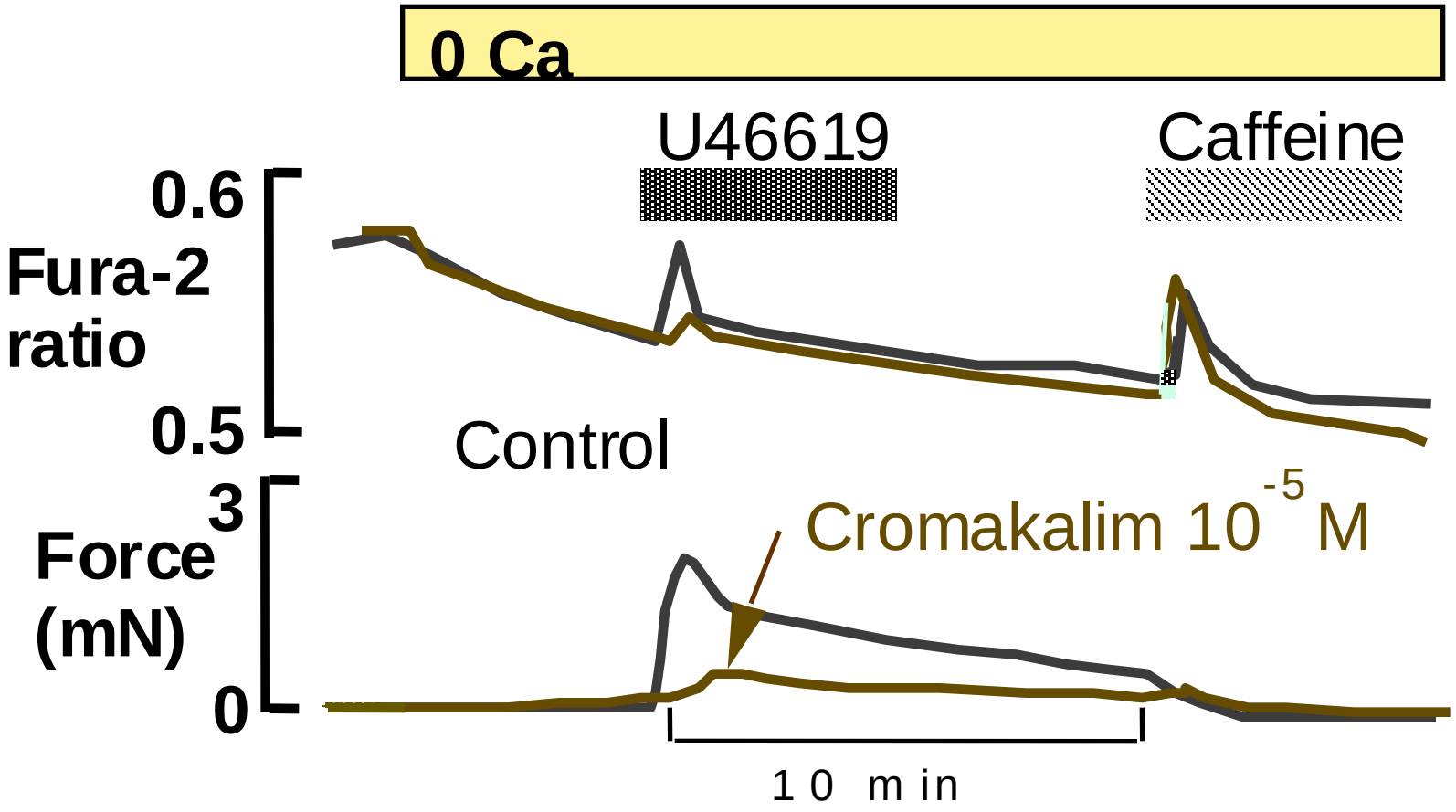
Agonist contraction & KCl depolarization



Relationship between $[Ca^{2+}]_i$ and force of contraction induced by serotonin ($10^{-6.5}$ M) in the absence (○) and presence of levcromakalim ($10^{-5.5}$ M, ●) or nicardipine (■).

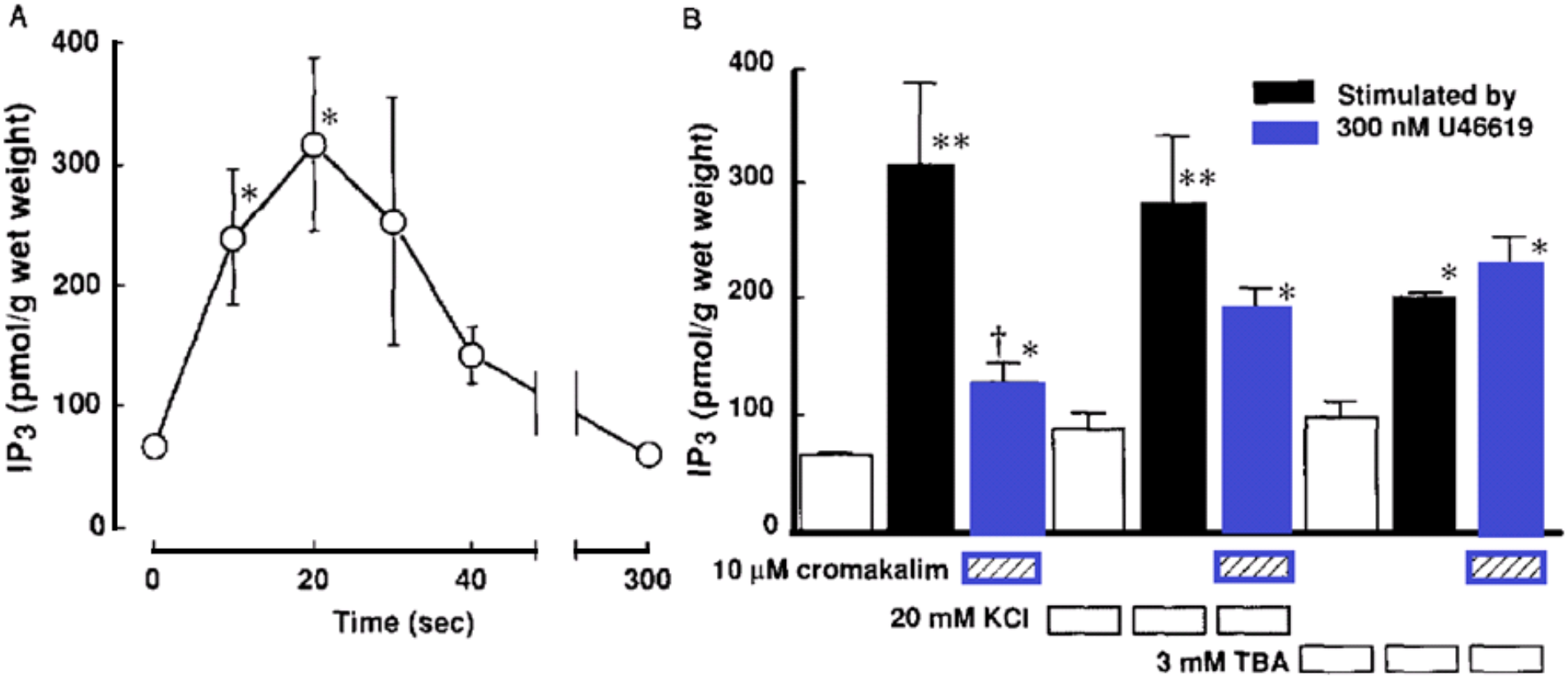


K^+ channel opener inhibits IP_3 generation & Ca^{2+} release from SR by a thromboxane A_2 analogue. **Hyperpolarization-relaxation coupling**



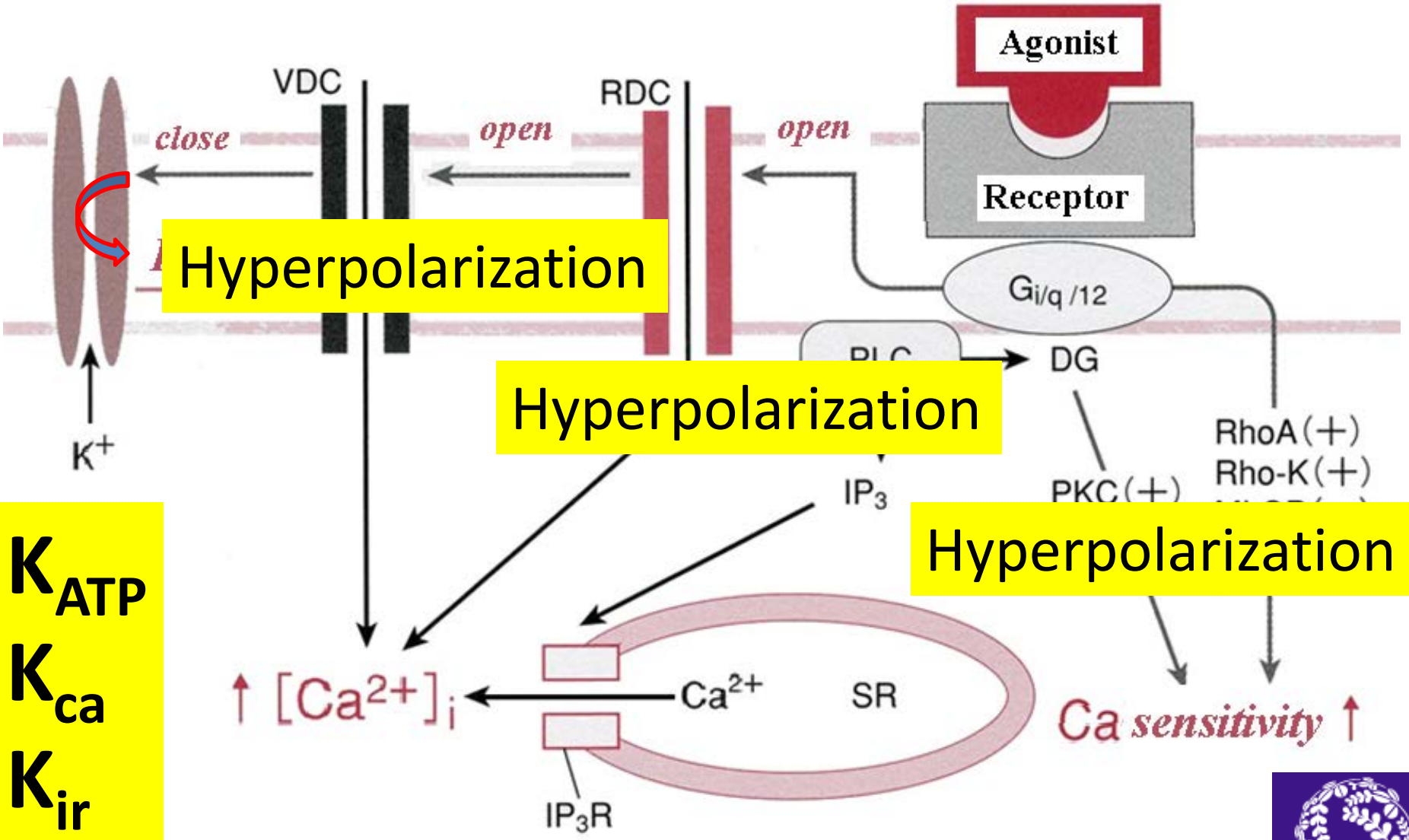
Naunyn-Schmied. Arch. Pharmacol. 1992;346:691-700.
Biochem. Biophys. Res. Commun. 1992;187:1517-22.

Activation of phospholipase C by the agonist U46619 is inhibited by cromakalim-induced hyperpolarization in porcine coronary artery. （in the absence of $[Ca^{2+}]_o$）



Yamagishi T et al.: Biochem Biophys Res Commun 1992;l87:1517-1522

Molecular signal mechanisms of **relaxation** of vascular smooth muscle via Hyperpolarization



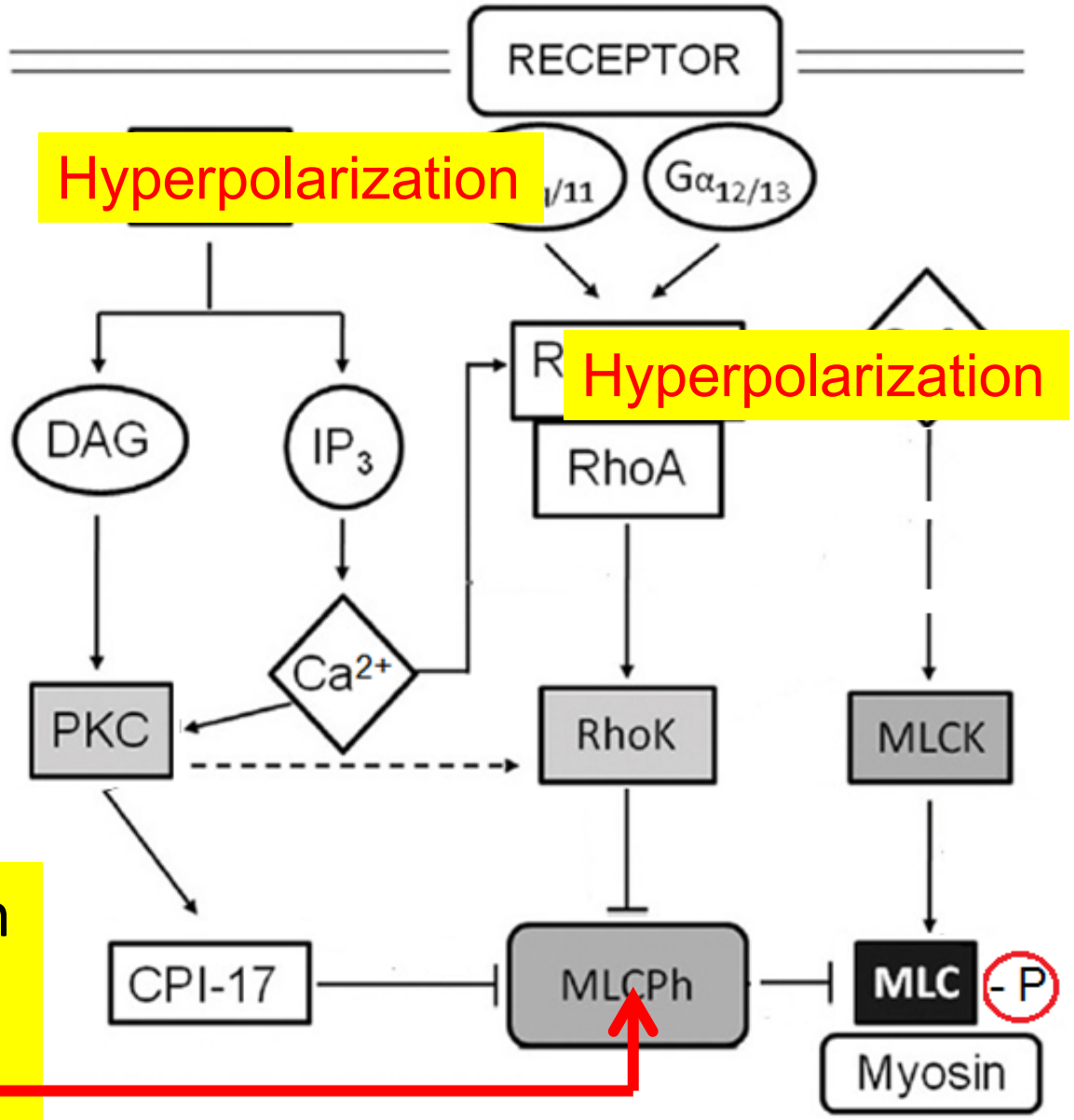
TOHOKU UNIVERSITY

Hyperpolarization decreases Ca sensitivity

KCO
Nicorandil
Nitroglycerin
EDHF

K_{ATP}
K_{ca}
K_{ir}

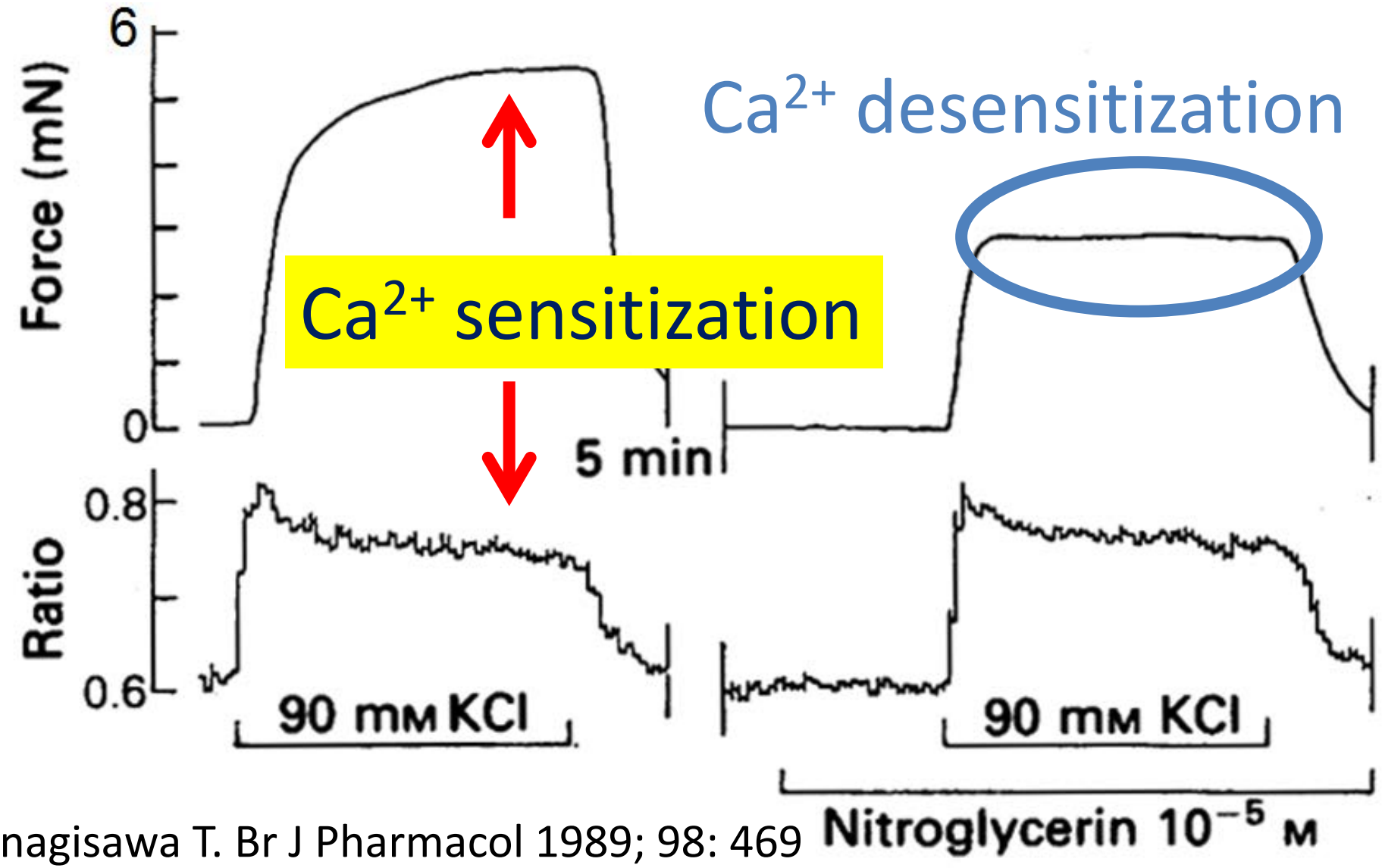
as NK hybrid



Nicorandil, Nitroglycerin
↓
NO→cGMP→G kinase

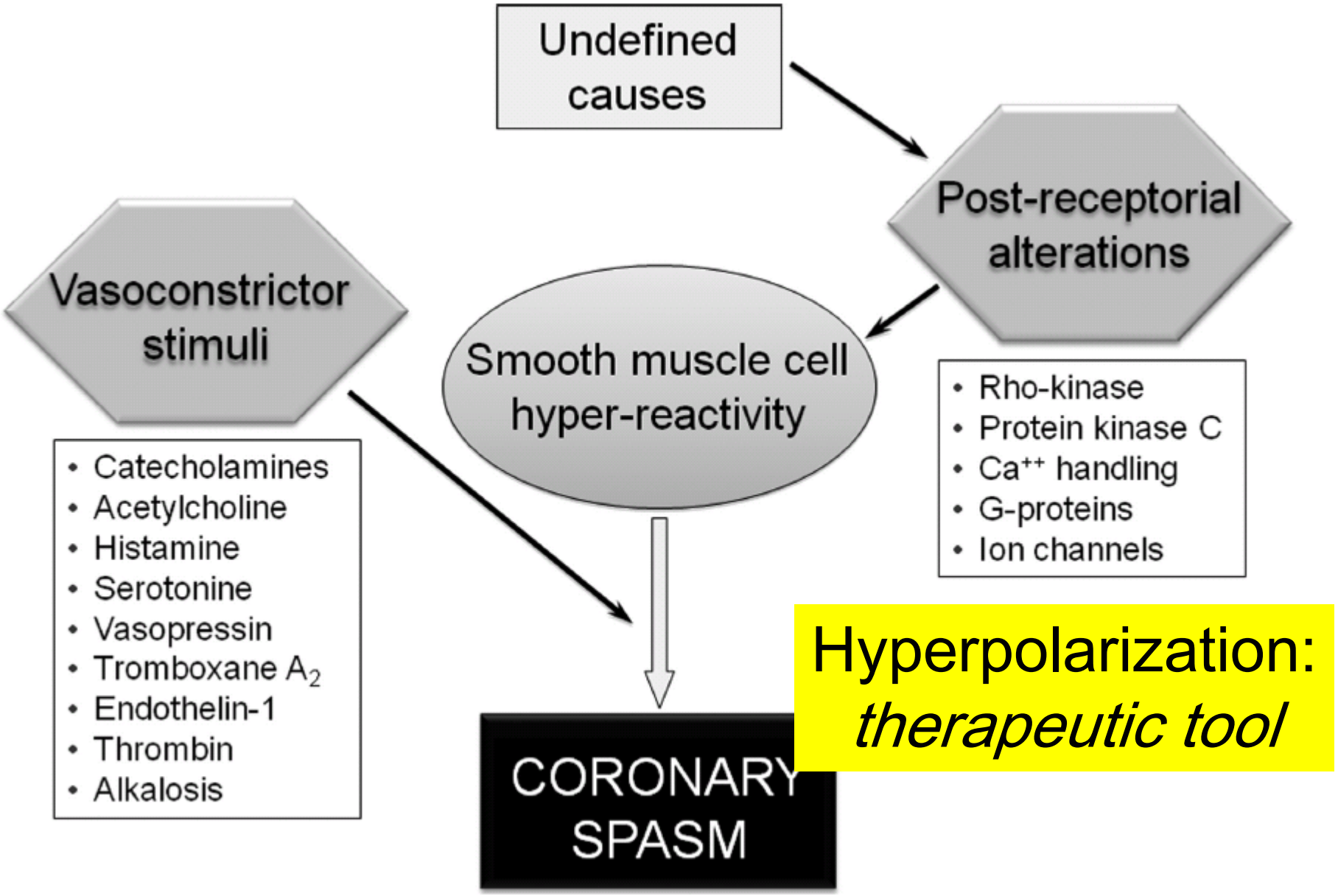
Circulation 2011;124:1774-82 (modified)

In the presence of nitroglycerin, Dissociation of $[Ca^{2+}]_i$ & Fc



Yanagisawa T. Br J Pharmacol 1989; 98: 469

Pathogenic mechanisms in coronary artery spasm.



Circulation 2011;124:1774-82

【Conclusion-2】

Coronary artery spasm mechanisms.

Ca^{2+} sensitivity in vasc. sm. m. is increased or decreased by depolarization or hyperpolarization, respectively.

The concept of **hyperpolarization-relaxation coupling** *via*. KCO or EDHF is very important, since we have precisely known the molecular mechanisms of **vasospasm**.

TOHOKU UNIVERSITY SCHOOL OF MEDICINE · SENDAI · JAPAN FOUNDED 1872

TOHOKU UNIVERSITY

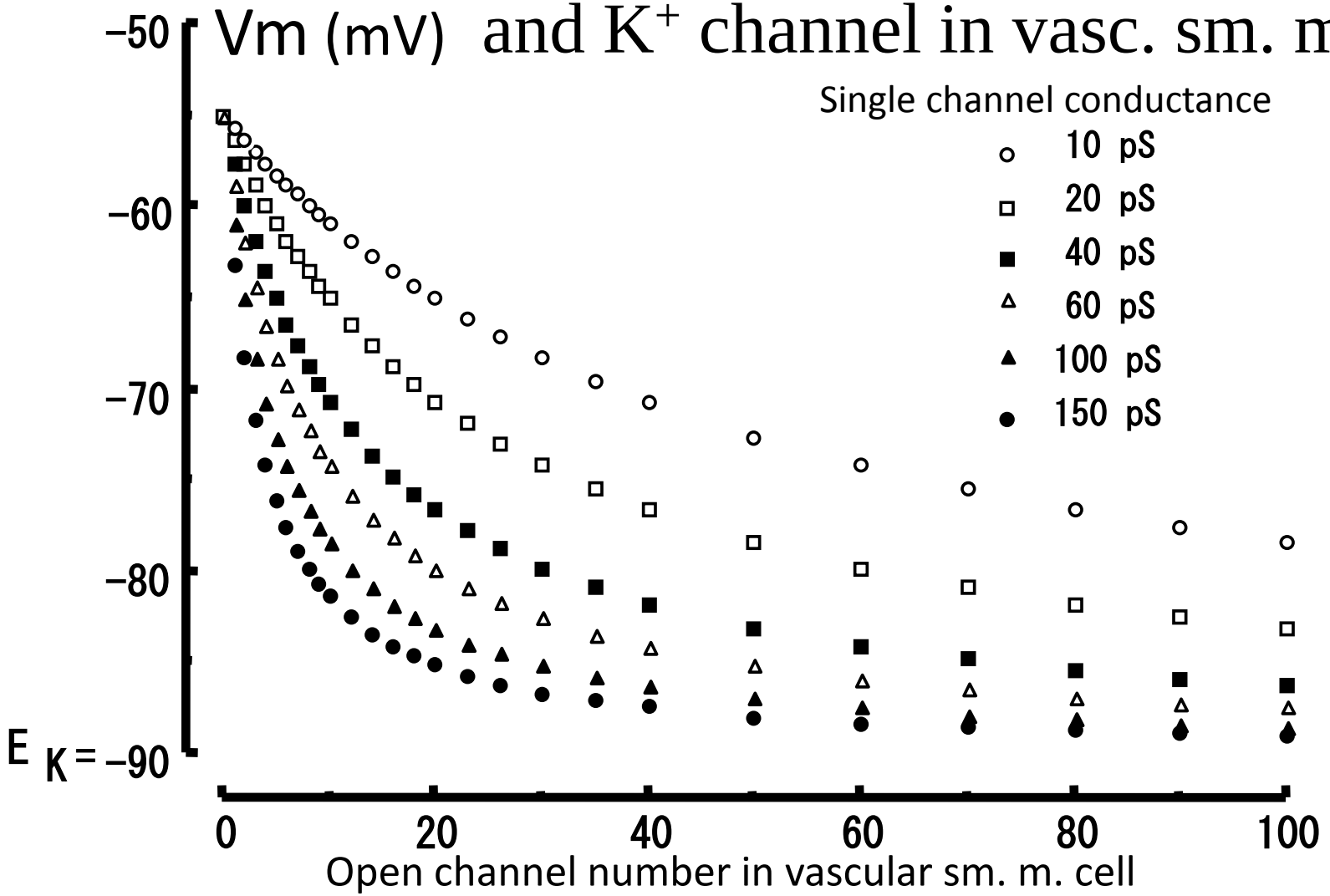
K^+ channel openers (K_{ATP}COs)

- Historical points of view
- Why they are **not** successful for the antihypertensive agents?
- Vasospastic angina
- Hyperpolarization-relaxation coupling
- Progress of new types KCOs

【Appendix】
The future of K_{ATP}COs & other type of KCOs

- Organ perfusion preservation of organ transplant
- Pulmonary arterial hypertension; *Sahara M et al. PLoS One. 2012;7(3):e33367. doi: 10.1371/ journal.pone.0033367.*
- Advanced diabetic nephropathy; *Tanabe K et al. Am J Physiol Renal Physiol. 2012;302:F1151-60.*
- Peripheral vascular diseases

Vm (mV) and K^+ channel in vasc. sm. m.



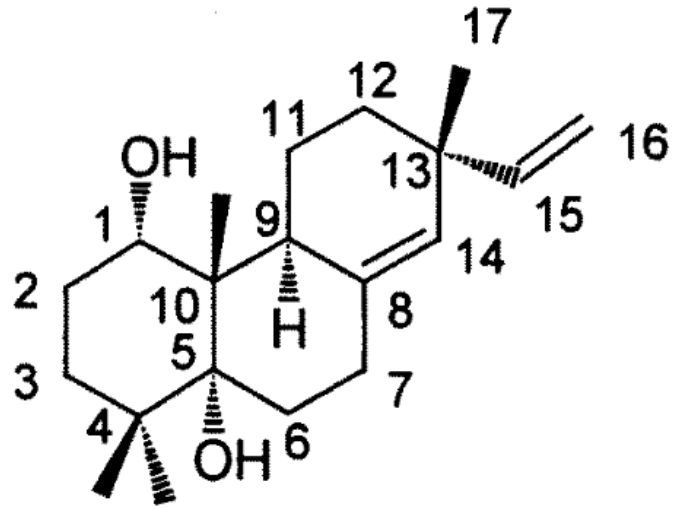
BK_{Ca}, IK_{Ca} ～100 pS, ～60 pS

K_{ATP} ～100 pS, ～10 pS

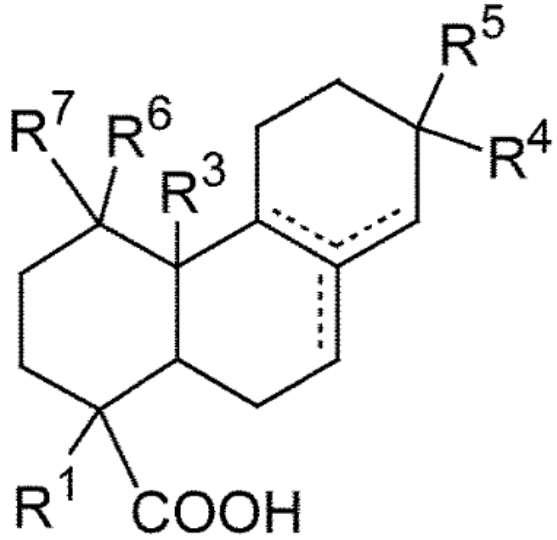
Kv ～10 pS

Folia Pharmacol. Jpn. 1995;106:157-69.

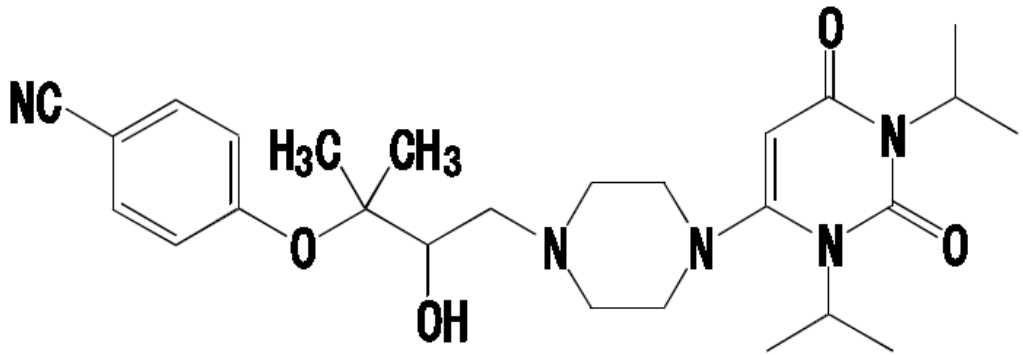
Other types KCOs



Maxikdiol

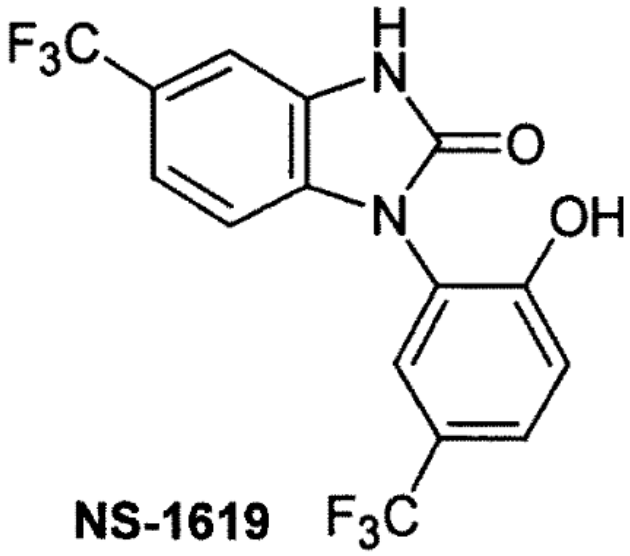


一般式（Ｉ）今泉祐治, 大和田智彦
特許第3973561号 カリウムチャネル開口薬



MS-12-709

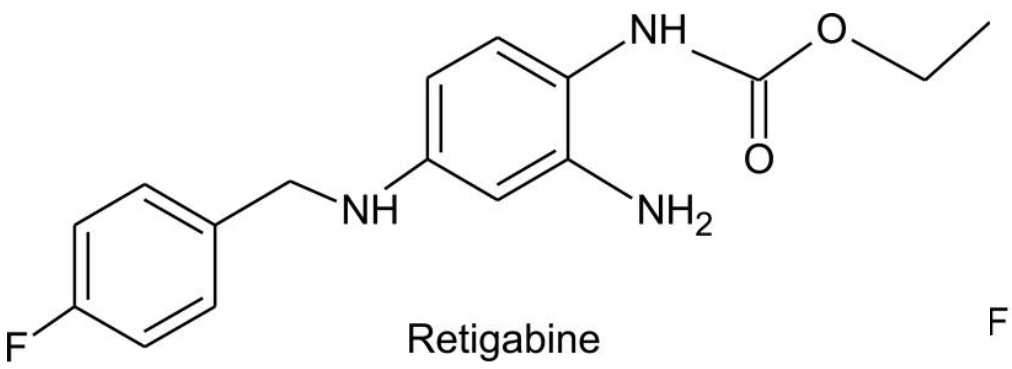
三井化学株式会社 海宝龍夫（ニフェカラント開発の過程から）
http://www.ehime-u.ac.jp/~achem/seminar/gist/57_2.pdf



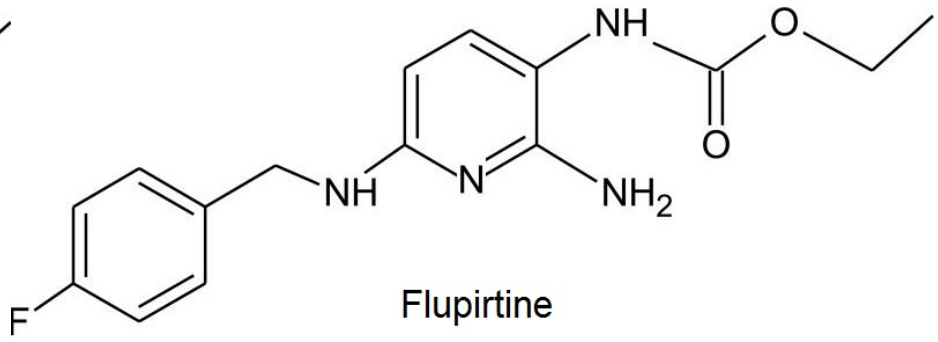
NS-1619

Anticonvulsant, Analgesic

- Ezogabine (Retigabine): KCNQ/Kv7 opener, anticonvulsant.
- Flupirtine: the same mechanism , non-opioid analgesic, muscle relaxant and anticonvulsant.



Retigabine



Flupirtine

Thank you for your attention!

20130412 教室の外で